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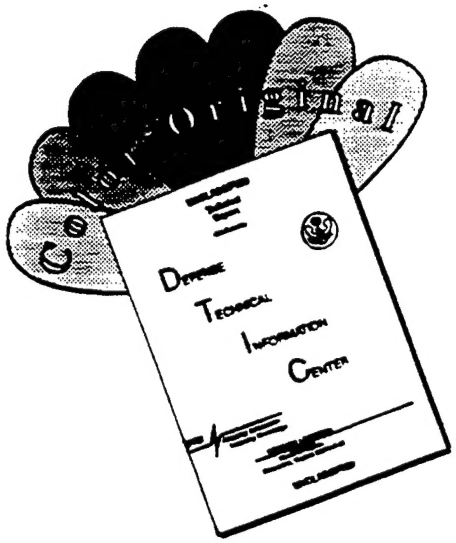

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Roger L Gibson, Major, USAF, BSC

University of Washington

Abstract

Primary Prevention of Acute Respiratory Infection Among United States Air Force RecruitsThrough the Use of Antimicrobial Handwipes -A Randomized Clinical Trial

By Roger L. Gibson

Chairperson of Supervisory Committee: Professor E. Russell Alexander
Department of Epidemiology

This double-blinded randomized clinical trial was performed to determine the efficacy of antimicrobial handwipes in reducing acute upper respiratory infections among United States Air Force Basic Military Trainees and in changing the prevalence of Group A Beta-hemolytic *Streptococcus pyogenes* (GABS) positive throat cultures.

The study was conducted in two phases. During Phase I, forty recruits were block randomized into four groups of ten subjects each. Two groups used antimicrobial handwipes containing parachlorometaxylenol (0.5%) and alcohol (40%); with one group additionally using hand soap containing triclosan. A third group used placebo handwipes containing water and lemon juice, and a fourth group continued normal handwashing practices. Bacterial hand counts were determined.

In Phase II, fifty groups (each consisting of approximately 53 recruits) were block randomized to use either the aforementioned antimicrobial or placebo handwipes during the six-week basic military training period. From medical records and questionnaires, data on sick-call visits were collected. Using pharyngeal specimens

collected at the beginning and end of training, changes in GABS positive throat culture prevalence were recorded.

Findings from Phase I of the study, showed antimicrobial handwipes, when compared to either placebo handwipes or normal hygiene practices, produced a highly significant 71.4% reduction in hand colony counts (p-value > .001). The addition of triclosan hand soap did not significantly change hand colony counts among those using antimicrobial handwipes (p-value = 0.38).

During Phase II, antimicrobial handwipes lowered the incidence of initial sick-call visits for acute upper respiratory infection by 32.7 percent (p-value = 0.02) and visits for sore throat by 40 percent (p-value = 0.01). GABS positive throat culture prevalence tripled (0.8% to 3.0%) during the training period for flights assigned to placebo handwipes, while the prevalence remained unchanged (1.2%) for those assigned to antimicrobial handwipes.

These data suggest antimicrobial handwipes may prove an effective method of reducing direct contact transmission of pathogens in high risk groups.

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Doctoral Dissertation

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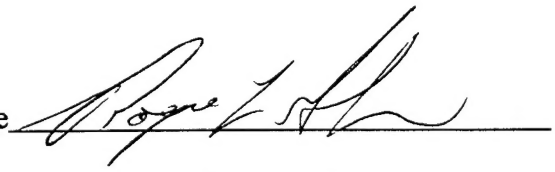
Signature 

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Primary Prevention of Acute Respiratory Infection Among United States Air Force Recruits Through the Use of Antimicrobial Handwipes -A Randomized Clinical Trial

by

Roger L. Gibson

A disseration submitted in partical fulfillment
of the requirements for the degree of

Doctor of Philosophy

University of Washington

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DEDICATION

I would like to dedicate this dissertation to Miles Lloyd Gibson. A man who, after seeing me through forty-five years of life and twenty-five years of formal education, remains my hero.

Chapter I

Background and Significance

1. Introduction

Despite improvements in treatment and advances in environmental engineering, including indoor air quality enhancements, acute upper respiratory infections remain a major cause of morbidity in the United States. Colds alone accounted for 190 million days of restricted activity and 40% of the sick time lost in the American workplace[1]. With respect to the military, where the availability of a continually ready force for national defense is imperative, the effects of such infections are potentially critical. For example, the loss of a number of pilots to the effects of cold viruses could prove the weak link in a military operation and lead to the loss of many lives, both military and civilian. Efforts are needed to identify effective methods of controlling the spread of upper respiratory illnesses. Military recruits, known at high risk for acute upper respiratory infection, comprise one group where control measures can be studied.

The work presented here represents an effort to determine the efficacy of an antimicrobial agent, delivered via the use of disposable handwipes, in interrupting the spread of pathogenic agents associated with acute upper respiratory infection in United States Air Force trainees. The results of the this study may lead to changes in procedures throughout the Department of Defense and substantial reductions in disease rates. Additionally, the practices tested in this trial may have broad applicability in other high-risk populations such as nursing homes, child care centers and public schools.

2. Military Recruits as High Risk Group for Infection

Military recruits are a mixture of young men and women from throughout the United States and its territories. Representative figures from the Army in 1990 show that recruits range in age from 17 to 35 years of age, with approximately 77% below 21 years. Twenty-six percent are female, 54% white (non-Hispanic), 34% black (non-Hispanic), and 5% Hispanic. Greater than 95% of recruits have graduated from high school and over 25% have attended college[2]. Due to the requirement for physical examinations prior to qualifying for enlistment, they are basically healthy, with few chronic conditions when they arrive at their first base and begin basic training. As a group, however, recruits have high rates of infectious disease when compared to their civilian counterparts or other military members.

Exact figures on the total number of infectious illnesses suffered by recruits are difficult to obtain from the literature. Although several studies have focused on the specific infectious agents, limited recent information is available on infectious diseases as a whole in this population. A ten year profile of infectious and parasitic diseases among hospitalized Navy personnel specifically addresses the infectious disease picture of recruits[3]. However, since some conditions such as acute respiratory disease often do not require hospitalization, these data may not represent a true picture of the relative importance of certain diseases. Additionally, communicable disease control measures used in recruit populations frequently involve the hospitalization (quarantine) of infected members. In many cases, if civilians of the same age as recruits or non-recruit military members were to develop the same infection, they would not be hospitalized but simply

told to stay home. Therefore, it is likely that the rates for conditions such as chickenpox may appear high for recruits when compared to other populations.

An older Navy study addressed recruit illnesses and used 'sick-list' data to quantify the proportion of illness due to disease classes[4]. According to the study, being placed on the sick-list meant that an individual had sought medical care and was determined to be ill by the attending health care provider. As such, the information obtained should be representative of a wide spectrum of illnesses suffered by recruits. Since this study was published in 1970, disease prevention changes, including the use of adenovirus vaccine, have occurred. These changes have likely altered the recruit illness profile. However, using the information from both studies mentioned above, and others, a reasonably accurate picture of the infectious diseases in recruit populations can be obtained.

Respiratory diseases are the major cause of infectious disease illnesses among military recruits[5]. With rates exceeding 200/100,000 person years, viral (primarily respiratory) illnesses are the number one reason for recruit hospitalization. Recruits are 5 times more likely to suffer a pneumonia hospitalization than military members with more than 3 years of service and 29 times more likely have a pneumonia hospitalization than non-recruits of the same age[6]. Prior to the introduction of adenovirus vaccines in the early 1970's, respiratory illnesses represented over 60% of overall sick-list medical conditions reported by recruits. Although the proportion of recruit illnesses associated with respiratory disease today are probably somewhat lower, they still represent a significant disease threat.

It is estimated that approximately 60% of Navy military recruits develop an acute respiratory illness during basic training and 30% seek medical attention for the condition[6]. The Army and Marines report similar rates of acute respiratory illnesses. Although the rate of acute respiratory illness among Air Force recruits is assumed to be comparable to that of the other services the latest reports indicate that about 10-15% seek medical care for acute respiratory illness during their period of basic training[7].

Although not well described, the pathogenic organisms involved in recruit respiratory illnesses likely do not differ from those affecting non-recruit populations of the same age in the United States. They include: *Mycoplasma pneumoniae, Haemophilus influenza, Streptococcus pneumoniae, Streptococcus pyogenes, Moraxella catarrhalis, Chlamydia pneumonia, Legionella pneumophila, Mycobacterium tuberculosis, Bordetella pertussis,* rhinovirus, adenovirus, influenza virus, respiratory syncytial viruses, and parainfluenza viruses[6].

Influenza and adenovirus deserve a special mention. Both have been associated with epidemics of respiratory disease among military populations, including recruits. Prior to routine immunization for Influenza A and B and Adenoviruses 4 and 7, these infectious agents were considered to cause 70% of all recruit respiratory illnesses[6].

Streptococcus pyogenes, a bacterial agent associated primarily with pharyngitis, appears to be a reemerging threat to military recruits. Outbreaks of streptococcal pharyngitis are common among recruits and hospitalization rates are around 20/100,000[3]. Historically important, *Streptococcus pyogenes* was the cause of and rheumatic fever outbreaks among military populations prior to the advent of penicillin.

In the 1980's the unexplained re-emergence of more virulent *S. pyogenes* caused numerous epidemics of acute rheumatic fever (ARF) in U.S. populations[8]. The Navy and the Army suffered their first ARF epidemic in 20 years[8,9]. These virulent strains also caused epidemics of pneumonia among U.S. Marines and cases of necrotizing fasciitis, polymyositis, peritonsillar abscesses and *S. pyogenes* sepsis. The military responded by adjusting prophylaxis strategies[10,11]. Shortly after the U.S. ARF outbreaks, virulent *S. pyogenes* strain were found associated with a syndrome of rapid multisystem failure often leading to shock and death. termed streptococcal toxic shock syndrome (STSS).

The epidemics of severe *S. pyogenes* have caused national concern and have frequently been the subject of sensational news reports. STSS was particularly alarming in that it affected previously healthy persons in an unpredictable and rapid fashion. Disease progression was often so rapid that treatment, which frequently included aggressive surgical debridement, could not keep ahead of soft-tissue destruction.

The new strains express a number of toxins or superantigens that partly explain their virulence, but the combination of host and bacteriologic characteristics that permit their aggressive invasion have not been totally defined[10-14].

Data regarding the impact of these virulent *S. pyogenes* strains have had upon military populations are clouded by nonspecific diagnostic codes, poor clinical recognition of new syndromes, lack of uniform definition of STSS and lack of uniform surveillance. Despite the problems in determining the exact impact of *S. pyogenes* disease, limited data demonstrate that the Department of Defense suffers from these *S. pyogenes* infections.

Table I. provides data on Navy hospitalizations for specific *S. pyogenes* infections from 1981-1993[4].

These figures may underestimate the true annual counts of disease since they are dependent upon hospital laboratories, clinicians and hospital admissions coders recognizing *S. pyogenes* as the etiologic agent. Otherwise, admissions are coded with more general diagnostic codes. Nevertheless, these data demonstrate that *S. pyogenes* has a significant impact upon Navy personnel. Data from U.S. Army and U.S. Air Force likely yield similar results.

In the winter of 1994, three trainees at San Diego's Basic Underwater Demolition School (SEAL trainees) were hospitalized with severe infections from *S. pyogenes*, and at least one was diagnosed with STSS [15]. Military recruits at Ft. Leonard Wood (Army) and Lackland Air Force Base and other U.S. military camps have additionally suffered from *S. pyogenes* infections, some of them severe. At Lackland AFB, an *S. pyogenes* outbreak within a single squadron led to the hospitalization of three trainees; one of which died from the infection [16].

These recent outbreaks of severe *S. pyogenes* infections will likely continue to affect military populations. Should *S. pyogenes* develop resistance to prophylactic penicillin therapy often given in recruit camps, then the Department of Defense (DoD) could experience outbreaks that rival those occurring in recruit camps before the advent of antibiotics in which thousands suffered infections each year. Such resistance is expected to occur soon [17].

Table 1. Range of the number of active duty Navy personnel hospitalized each year, 1981-93 for Group A Beta-hemolytic *Streptococcus pyogenes* associated conditions

	Range
Peritonsillar abscess	171-355
Streptococcal pyogenes septicemia	3-10
Acute rheumatic fever	6-15
Streptococcal pyogenes pneumonia	5-38

(Naval Health Research Center, San Diego)

Other infectious diseases are seen at high rates among basic trainee populations. Table 2 provides a listing of these diseases and their hospitalization rates[6].

Several factors appear related to the high risk for infectious diseases, including acute respiratory disease, experienced by recruits. Primary among these are the unique characteristics of the training process itself.

The Mixing of Young Adults from Many Regions

Basic military training is an uncommon experience in many ways. For one thing, it provides an opportunity to bring together large numbers of people from diverse social and geographic backgrounds. The mixing of these people, some carrying unique strains of regional pathogens, provides an opportunity for exposure to a wide variety of diseases. As such, recruits are very likely to encounter pathogens to which they have never before been exposed.

During childhood, many disease exposures occur as children encounter other children and adults; both in and outside of the family. Shortly after reaching school age, they reach a point where they have acquired immunity (either through vaccination or by actually getting the disease) to most of the diseases of those living around them. For many diseases, a level of herd immunity provides them with some protection. Only if they move to another area (or have an infected person move into their area) do they become exposed to new pathogens. While it is true that Americans represent a rather mobile society, in most cases, the relocation of persons or families occurs in small units. Consequently, the introduction of a few new people into a community, usually does not result in rapid changes in the communities disease profile. Exceptions exist; when highly communicable

Table 2. High risk diseases among military recruits and associated hospitalization rates

Disease	Hospitalization Rate (Person years)
Respiratory infections	200/100,000
Intestinal infections	150/100,000
Ill defined intestinal infections	118/100,000
Bacterial food poisoning	5/100,000
Non-protozoal intestinal infections	27/100,000
Pulmonary tuberculosis	25/100,000
Chickenpox	64/100,000
Measles	75/100,000
Rubella	155/100,000
Infectious mononucleosis	75/100,000
Viral hepatitis	118/100,000
Meningococcal infections	3/100,000

Gray G.C. Federal Register 1995

diseases, such as measles, are introduced into remote immuniologically naive populations, outbreaks can occur. Cases mount up rapidly until a sufficient number of susceptible people no longer exist to continue the outbreak. With less highly communicable diseases, it is likely that the introduction of an infectious individual into a new community will result in few exposures. It is possible for the new agent to die out rather than become established in the community.

In recruit populations, however, many people come together at once. Because of their geographic diversity, it is highly likely that a person, suffering from an illness due to a disease strain with a regional distribution, will encounter persons who are susceptible to the strain and they will become ill. The housing environment of recruit training also helps to perpetuate illness associated with unique strains of disease.

Stress Induced Lowered Immunity

The basic training experience is stressful. Movie depiction's of tough drill sergeants, long work days, and intense physical activity are realistic. The physical and emotional stresses of basic training are likely to take a toll on a recruit's resistance to infection. Suppression of the immune system has been shown to be associated with recruit training[18]. Comparisons of blood samples collected at the beginning and mid-point of basic training showed T-cell counts reductions among Navy recruits. While these reductions may be due to the stress of the training regime or to exposure to multiple antigens during the immunization process, the ultimate result is a lowered resistance to infection.

Increasing Number of Unvaccinated Recruits

Recent studies have shown decreasing immunity to childhood diseases among young adults[19-24]. Several measles and rubella outbreaks have occurred on college campuses and in office buildings. Investigations of these outbreaks revealed that a significant numbers of young adults were not properly immunized as children. Through successful immunization programs after the licensing of rubella, measles, mumps, tetanus and diphtheria vaccine, the incidence of these illnesses was drastically lowered in the United States. Many parents, possibly believing that these diseases were eradicated, failed to get their children immunized. Kelly et al.. showed, among U.S. Army recruits, the seronegativity rates for childhood diseases was 20.7% for measles, 17.5% for rubella, 15.6% for mumps, 6.9% for varicella and 14.65 for poliovirus type three[2]. In the crowded, mixed, and stressed environment of recruit training, it is hardly surprising that cases of these childhood diseases occur.

Measles and rubella vaccination (or proof of immunity via serology) have long been standard practice at recruit training installations. The cases of measles and rubella seen today likely occur either because the recruit was only recently immunized or not yet vaccinated pending serology results. In either case, exposure to the disease took place prior to immunization.

Authorities are considering administering mumps and varicella vaccines to recruits. Arday et al.[25] showed that it would be cost efficient to give mumps vaccine. Gray[18] pointed out that the hospitalization rate for varicella among recruits increased four fold from 1980-1988. He concluded that this is likely due to decreasing immunity

among American children. Other varicella outbreak investigations among military recruits have shown an association with enlistees from temperate regions such as Puerto Rico[26,27]. The recent licensing of varicella vaccine may lead to its use in selected recruit populations.

Housing and Crowding

Traditionally recruits are housed in barracks. Consisting of large open bays containing cots, clothing lockers, and little else, the barracks provides an inexpensive means of housing large numbers of people. From a training standpoint, barracks living is considered to promote the team building concepts on which current military doctrine is grounded. From an infectious disease standpoint, the barracks environment represents a rather ideal opportunity for disease spread. With no wall to physically separate people, frequent direct and airborne contact can occur. As might be expected, the incidence of disease (particularly respiratory disease) increases as crowding increases. Understanding this important relationship, medical and military leaders have worked to establish proper guidelines on the amount of space required for each recruit. Over the past two hundred years, many changes in space requirements have occurred[28]. Current requirements call for 72 square feet of floor space per recruit.

Modern recruit housing also plays a role in the pathogen exposure. New building construction frequently is aimed at energy efficiency. Consequently the amount of recirculated air within a building is increased to avoid heat loss in the winter or the loss of cooled air in the summer. Brundage, et al. found the risk of respiratory disease among

recruits was 50 percent higher for those housed in new 'tight' buildings compared to those housed in older structures[29].

The primary reason barracks living and crowding increase the acute respiratory disease risk for recruits is directly related to the modes of transmission of these disease causing organisms.

3. Methods of Pathogen Transmission

Uncertainty exists regarding the exact transmission mechanism of many organisms capable of causing acute respiratory disease among recruits. Three routes are considered plausible: inhalation of small particle infectious nuclei capable of remaining suspended in air indefinitely; inhalation of large droplet infectious nuclei that remain in air for shorter periods; and direct contact with infected persons and their secretions[30]. While little is known about which of these transmission mechanisms is the most prevalent for a given organism, all respiratory pathogens are considered capable of spreading by direct contact[31].

The respiratory secretions of an infected person contain large numbers of organisms[32]. These secretions are capable of contaminating the skin and clothing of the infected person. By touching objects with contaminated hands it is possible for the infected to person to 'seed' infective organisms over a wide area. Direct contact transmission occurs when a susceptible person touches a contaminated surface and then transfers the infective organisms to his eyes, mouth, or nose. Hand sanitation is directed at stopping direct contact transmission by killing disease organisms on the hands.

Besides by direct contact, an infected person contaminates the environment by breathing, coughing, sneezing, spitting, singing and even talking[32]. Respiratory secretions are expelled by these actions and contaminate the air with droplets containing infective organisms. The expelled droplets vary in size. Large droplets travel only a short distance (2-3 feet)[33] and may serve as source of contamination for skin and other objects. These, in turn, may be touched by hands and transferred to the face, nose and mouth. If in close proximity to the infected person when he cough or sneezes, large droplets may be directly inhaled and infect a susceptible host. The smallest droplets evaporate immediately after being expelled and while still in the air. These infective particles, along with other substances found in respiratory secretions, form droplet nuclei which are so small (1 to 3 μm) that they may remain suspended in the air indefinitely[32]. The droplet nuclei may be inhaled by susceptible individuals and ultimately lead to an acute upper respiratory infection. To cause an infection, however, sufficient numbers of organisms must be inhaled to reach an infective dose. Airborne transmission occurs almost exclusively indoors. When an infected person releases infective droplet nuclei into the air, the particles disperse as the air circulates. In confined indoor atmospheres, it is possible for concentrations of droplet nuclei to reach infective dose levels. As such, ventilation plays a critical role in the spread of acute upper respiratory infection via droplet nuclei.

Ventilation provides a means by which fresh air replaces existing (stale) air within a room, building, or any confined space[34]. Using the principles of dilution, ventilation systems within a building provide for the comfort of the building residents by removing

odors, moisture, noxious gases, and smoke. The principles of dilution also serve to lower concentrations of organisms associated with the airborne transmission of acute respiratory disease. As the number of infective particles per cubic meter of air decreases, the probability that a susceptible individual will receive an infective dose also decreases.

The relative importance of ventilation in the transmission of disease depends on specific organisms and the role droplet nuclei play in their spread. In general, for droplet nuclei to be important, the disease organism must be able to survive outside the host for extended periods, be infective at low doses or expelled into the air in large numbers, and resistant to sunlight and drying. For some diseases, particularly viruses, droplet nuclei appear to be the main route of transmission. Influenza is a good example. McLean showed that hospital patients exposed to 'treated air' (ultraviolet light) were less likely to develop influenza than those exposed to normal air[32]. Moser, in an investigation of an outbreak of influenza on board an commercial airliner, showed that 72 percent of the passengers became infected after a three hour exposure to one index case while the ventilation system of the plane was inoperative[35].

Adenovirus (Types 4 and 7) infections provide another example. Until the advent of effective vaccines, adenovirus was a major source of acute respiratory illness among military personnel. Characterized by a prominent cough, the infection leads to the formation of large numbers of droplet nuclei[36]. Studies conducted in the 1960's by Couch showed that the dose required for infection via the aerosol route was only 1/20th of that required for infection by direct contact[37].

For many acute respiratory disease agents direct contact transmission appears to be the most advantageous route. Rhinoviruses, likely the most common cause of acute respiratory illness, have been shown to spread very efficiently by direct contact[38]. In fact, Gwaltney et al. under experimental circumstances were unable to demonstrate airborne transmission of the virus. However, Dick et al. in another experiment, showed that rhinovirus can be transmitted via the aerosol route. He contends that droplet nuclei represent the major avenue of disease spread[39]. Considerable controversy remains over which route is the most important.

Direct contact is considered the primary means of transmission of other viruses, including respiratory syncytial virus, parainfluenza virus, and adenovirus types 1,2,3,5 and six[36]. With respect to bacteria, streptococcal infections are also considered to spread primarily through close contact, while *Bordetella pertussis* is transmitted primarily through droplet nuclei. As in the case of viruses, the fact that one route of transmission presents as the most common does not rule out the fact that other routes exist.

One of the significant factors associated with ventilation is humidity. Studies on influenza outbreaks and seasonal associations with disease incidence have led to inferences that pathogenic organisms survive better under conditions of low humidity[32]. It is possible to control humidity through modifications in ventilation. As such, ventilation may play a role by either increasing or decreasing the survivability of disease organisms in the environment which then can be spread by either airborne or direct contact routes. Additionally, low humidity environments may lead to drying and irritation of nasal and

ocular membranes. This may, in turn, allow infective organisms to more easily invade the mucosa and increase the risk of infection via direct contact.

The living conditions in basic military training not only increase the chances of airborne droplet exposure but also predispose the recruits to close physical contact[40]. The use of an intervention aimed at reducing or eliminating the spread of infectious organisms by direct contact, primarily hand to mouth/nose transmission, could potentially produce substantial benefits for recruits. By reducing the number of trainees infected by direct contact, overall infectious organism exposure within a training unit may be decreased. With fewer ill recruits per group the spread of disease by all pathways will be reduced. Fewer sick days, medical visits, and hospitalizations will occur; training time losses reduced, and training performance enhanced.

Several methods exist to reduce the spread of disease organisms by direct contact. In fact, the discipline of infection control is grounded in principles aimed at curtailing direct contact transmission[41]. Methods range from the use of gloves, gowns and masks, and aseptic surgical techniques; to handwashing with soap and water[42]. Within the military population, given the rigors of the occupation, the use of sophisticated techniques are of little or no practical value. Hand sanitation represents the most practical method available.

4. Evidence Supporting Hand Sanitation as a Control Method

Although many recent studies have shown the efficacy of specific handwashing protocols and products in lowering hand bacteria counts, there are reports from the literature where clinical measures were used. Studies showing a reduction in disease rates

associated with handwashing provide much stronger evidence of efficacy than reports of log reductions in bacterial counts from hand cultures.

Historically, one of the first studies showing that handwashing prevents the transmission of infectious diseases was published by Ingaz Semmelweis in 1847[43]. Dr. Semmelweis, a Hungarian obstetrician, had noted a marked difference in the rates of childbed fever deaths among women giving birth in two clinics. The First Clinic, attended by physicians, had a childbed fever death rate of 11.4%, while at the Second Clinic, attended by midwives, the death rate was much (1/3 to 1/4) lower. He postulated that the attending physicians (who also performed autopsies) were transmitting the infection via their hands to the delivering mothers. As the physician in charge of First Clinic, he issued orders that all doctors and students wash their hands in chlorine water after early morning post-mortum examinations. Within seven months of issuing the order, the death rate from childbed fever dropped from 12 to 3 percent.

Recent evidence from the literature of handwashing's effect on infectious disease transmission comes from two main sources; health care and community settings.

Health Care Settings

Health care providers, in the performance of their duties, may serve as a source of transmission of infections to patients. Handwashing is considered the most important procedure in preventing nosocomial infections. It is estimated that each year 1.5 million patients suffer a nosocomial infection with medical costs of around $1 billion[43].

A recent study showing that handwashing can impact infectious transmission compares the rate of methacillin resistant *Staphlococcus aureus* (MRSA) infections in two

neonatal intensive care units[44]. During a seven week trial, each unit used a different hand cleaning product. One unit used chlorhexine gluconate (Hibiclens®) while the other used triclosan (Novaderm®). With the exception of the change in handwashing products, all other practices on the two wards remained the same. At the end of the study period, the ward using triclosan had a MRSA infection (colonization) rate of 0.14 new cases per week (1 infection in 46 admissions) while the ward using chlorhexine gluconate had 3.4 new MRSA infections per week (p-value 0.0001). The proportion of MRSA infected infants in the unit using triclosan dropped from 41.7% to 11.7% during the trial period. Comparison of staff 'hand damage' during the trial period showed that those using triclosan experience fewer skin problems than those using chlorhexine gluconate. The authors of the paper believe the difference in MRSA rates is due to increased acceptability of triclosan by the staff; resulting in more frequent handwashing.

Another study in a hospital setting showing the effect of handwashing on disease transmission, concerns an outbreak of Respiratory Syncytial Virus (RSV)[45]. During a community-wide RSV outbreak, the researchers implemented procedures in the infant ward designed to reduce transmission. These included strict handwashing procedures, the use of gowns and the allocation of RSV infected infants and their staff into cohorts. Investigators compared the rate of nosocomial acquired infections among both infants and staff with those of the previous year. Results showed that the rate of nosocomial infection in the infants dropped from 45% during the previous year to 19% after control procedures were implemented. In staff members, the rate of infection increased from 42% during the prior year to 56% for the study period.

In this study, changes in handwashing were implemented as part of an entire set of procedures designed to reduce the transmission of RSV on the ward. It is impossible to separate the effects of handwashing from those associated with the other procedures. However, lending support to the effect of handwashing in reducing disease transmission is the fact is that the rate of infection of staff members (who would have close contact and possible aerosol exposure to infected infants) increased compared to the previous year, while the nosocomial RSV rate in the infants (to which the main source of exposure was through direct contact) decreased markedly.

In a case-control study of an outbreak of Hepatitis A in a Neonatal ICU unit showed how disease transmission can increase when handwashing procedures are lacking[46]. Among the 33 staff members who had contact with the index Hepatitis A case, 8 of 14, who reported never or rarely washing their hands after touching the infant, developed Hepatitis A. Only 2 of 19 staff members who reported washing their hands sometimes or often after touching the infant developed the disease (RR 5.4; $P < .01$). Additionally, the three infants who nosocomially acquired Hepatitis A during this outbreak were all exposed to the same nurse who also contracted the disease and reported infrequent handwashing.

The studies mentioned above point out how handwashing can impact the spread of infectious disease in a health care setting. They are based on the premise that the health care provider's hands serves as the mode of transmission in the high risk setting of the hospital; a circumstance where exposure to pathogens is likely and many of those exposed

(the patients) have compromised immune systems. Perhaps of more relevance is the role of handwashing in the transmission of disease in a community setting.

Community Settings

During a 36 week study period, Black et al., 1981[47]compared the incidence of diarrhea in non-toilet trained children attending four day care centers in Atlanta, Georgia. The four centers were comparable with respect to building design, number of employees, number of children; and age, sex, and race composition of the children enrolled. Changes in handwashing practices were implemented in two of the centers while the two other centers served as controls. Incidence of diarrheal episodes among attending children were tracked in the same manner for all four centers. Black found that the incidence of diarrhea per 100 children per week was significantly lower in the centers where handwashing procedures were implemented. While the rate was higher at baseline for the centers were handwashing procedures where implemented (16.3/100/week compared to 6.1/100/week in the controls) the rate during the study period was only half that of the control group (4.2 vs. 8.1). The most striking reduction occurred in children less than 18 months of age; possibly related to the effect of handwashing intervention on care givers who would have direct contact with children during diaper changing.

In a non-blind randomized trial in Rangoon, Han et al.[48] was also able to show that handwashing can effect the transmission on disease. Using approximately 500 children under 5 years of age from 350 households, the mothers and children from randomly selected households (1/2 of the 350 eligible households) were given soap and instructed to wash before preparing and eating meals and after defecating. The mothers

and children from the other households were not given soap or instructions. The children in all 350 households were followed for 4 months and rates of diarrhea and dysentery compared.

Among the children from households receiving the intervention, a 70% reduction in diarrhea episodes and a 40% reduction in dysentery episodes during the study period was reported. Most of the reduction was seen in children under 2 years. Studies in Bangladesh and Guatemala showed a similar impact on diarrheal disease when handwashing procedures were implemented[49].

Given the weight of evidence showing hand sanitation as effective method of controlling pathogen transmission, the importance of direct contact transmission in the spread on respiratory pathogens, and high military recruit acute upper respiratory infection rates, control methods aimed at improving hand sanitation among trainees could prove an effective means of lowering the incidence rates. Approaches applicable to military trainees must be simple to administer, effective and readily available. Although soap and water handwashing meets these requirements in that it provides a method of topical disinfection, conditions exist in basic training that may make its use problematic. The training regime frequently includes periods when recruits can only wash their hands once or twice daily. A portable, disposable and easy-to-use method of hand-cleaning could potentially increase personal hygiene and reduce infectious organism transmission. One way of accomplishing this goal would be through the use of antimicrobial handwipes.

5. Antimicrobial Handwipes

Antimicrobial handwipes are available in a wide variety of formulations. At least one company produces individually sealed packets containing one 6 x 7.5 inch premoistened wipe, containing a solution of 0.5% parachlorometaxylenol and 40% denatured ethanol[50].

Parachlorometaxylenol (PCMX) is a halogen-substituted phenolic compound[51]. It has been used for decades as an ingredient in disinfectants and antiseptics. In 1933, researchers concerned with maternal childbirth deaths due to *Streptococcus pyogenes* found that a 2% solution of PCMX killed the organisms within two minutes of exposure even in the presence of pus[52]. Recently PCMX has received widespread attention as an additive to handwashing products for health care providers in the United States[53]. The Merck Index reports PCMX has 60 times the antimicrobial activity of other phenolic disinfectants against a variety of gram-positive and gram-negative bacteria[54]. The Food and Drug Administration have approved its use in a wide variety of formulations including makeup, bath soaps, shampoos and deodorants[55].

Most of the research on the antimicrobial effects of PCMX consists of studies involving small numbers; less than fifty subjects[55-57]. In these studies, effectiveness was measured by reductions in bacterial counts taken either from treated skin or by 'glove juice' methodology; a method of obtaining total bacterial counts from hands. In the 'glove juice test, hands are placed in sterile gloves along with a collection media. After a specified contact time, an aliquot of media is collected and cultured on blood agar. Only one study was found where efficacy was determined through a comparison of post-

treatment clinical disease[58]. In that study, the treatment comparison was confounded by the concurrent application of prophylactic antibiotics.

The randomized clinical trial proposed in this project is the first to test the impact of the PCMX on clinical disease in a large number of subjects. This trial is also unique in that it is the first, to the investigators' knowledge, to clinically test handwipes as a method of delivering the antimicrobial agent. Because of the benefits of being both portable and disposable, handwipes have the potential of proving a practical solution to the military's problem of high rates of acute respiratory illness.

The findings of this study in a military recruit setting are applicable to other situations where individuals are in close contact with others. Settings such as nursing homes, child care centers, and schools create situations where the transmission of respiratory disease causing agents via direct contact is highly probable. Improved hand sanitation through the use of antimicrobial handwipes within such settings could lead to fewer infected individuals acting as sources of infection for other group members. At the same time, the residual effects of agents such as PCMX on the hands of uninfected group members could reduce the dose of pathogen organism to which each is exposed. The cumulative effect created by both infected and uninfected members of the group using antimicrobial handwipes should lead to fewer new disease cases.

Chapter II

Methods

1. General Study Design

The study was a two-part randomized, double-blinded clinical trial involving men and women undergoing basic military training at Lackland Air Force Base, in San Antonio, Texas. The first part of the trial compared the bactericidal capabilities of four hand-cleaning regimes. This laboratory-based trial, referred to as the 'glove juice' test, was intended to serve primarily as a decision making tool for the development of the second part of the trial. Bacterial colony handcounts were collected from the participating subjects at specific sampling times over a week-long period.

The second part of the trial compared handwipes formulated to contain antimicrobial agents with handwipes containing no antimicrobial agents. Using oropharyngeal specimens, medical records and questionnaires, the handwipe types were compared to determine their effect on acute upper respiratory infection incidence and the prevalence of Group A beta-hemolytic *Streptococcus pyogenes* (GABS) positive throat cultures.

2. Study Population

The study was conducted exclusively among United States Air Force military trainees. All Air Force enlisted personnel (approximately 34,000 per year) receive initial military training during a six-week basic training course at Lackland Air Force Base; the only such training center in the United States Air Force[59]. Arriving from geographically diverse locations, recruits are assigned to a unit called a squadron composed of

approximately 800 individuals who are housed in a single building. There are currently five active squadrons on the base complex. Although in close proximity to one another, each squadron contains its own command and support staff and are designed to function as a stand alone facility for the housing and education of assigned recruits. The map in Appendix 1 shows the location of the squadron with respect to one another and to the medical facilities.

Squadron buildings on Lackland AFB are identical three story structures. The bottom floor contains classrooms, dining facilities, administration offices and laundry facilities. Three of the five squadron house medical aid stations are manned by physician assistants and medical technicians. The two squadrons without medical aid stations are located less than fifty yards from a squadron with a medical aid station. The second and third floor each contain eight open bay barracks. Each floor in the squadron has a separate air handling system. With all windows sealed, the building's ventilation system provides complete environmental control.

The recruits in each squadron are divided into groups of approximately 54 members of the same sex called flights. Individuals within the squadron share a dining hall, classrooms, and laundry facilities. Members of a flight live in large two-room open bay barracks and sleep in single beds spaced three feet apart[60]. The flight members share bathroom and shower facilities co-located to the open bay barracks.

Each flight is paired with another from the same squadron (referred to as brother or sister flight) that began training on the same day. Whenever possible these flights are matched by gender. Flight members interact closely with one another and to a lesser

degree with the members of their brother or sister flight. Very little interaction occurs between other flights in the same squadron. There is virtually no contact between recruit members of separate squadrons.

Recruits arrive weekly on Thursdays and Fridays to begin their training program. Training begins the Monday following their arrival. During the three to four days prior to the beginning of training, the recruits receive military clothing, undergo orientation, and submit to medical processing. As part of initial medical processing, trainees routinely receive vaccinations for influenza, meningococcal meningitis, tetanus and diphtheria. They are serologically tested for rubella and rubeola. Sickle-cell, glucose 6 phosphate dihydrogenase and tuberculosis screening tests are conducted. Females receive blood human chorionic gonadotrophin (HCG) tests to determine pregnancy status. Recruits who have not received a Human Immunodeficiency Virus (HIV) screening test within the last six months are so tested. Unlike other military services, Air Force trainees receive no routine antimicrobial prophylaxis at the beginning of training[61].

On the Sunday prior to beginning formal training, medical technicians travel to the squadrons to determine the results of the tuberculosis test. At the end of the first training week, recruits return to the medical processing area to receive oral polio vaccine. Rubella and rubeola vaccine is administered to those with non-immune status as determined from serologic testing[62].

Throughout the training period, recruits are provided with an antimicrobial hand-soap. However, no detailed instructions are given on the use of the soap in handwashing and no mandatory handwashing requirement is prescribed. As part of their training, all

recruits attend a class in basic hygiene where issues related to cleanliness and sanitation are covered in minimal depth[63].

During the training period, approximately four percent of recruits are removed from a given flight due to medical, behavioral or administrative reasons[64]. These recruits are reassigned to a separate squadron building referred to as Medical Hold. This squadron serves as a holding area pending further disposition. Sixty-four percent of these recruits are ultimately separated from military service[65]. After a period of recuperation and treatment, the remaining recruits are assigned to new flights and reenter training. During the period in Medical Hold, recruits have no interaction with those who continue training.

Approximately three percent of the recruits in a given flight fail performance standards and are reassigned to another flight within the same squadron. Normally the flight to which the trainee is assigned began training one week after his or her original flight[65].

Military recruits, and Air Force trainees in particular, provide an optimum population in which to conduct this clinical trial. Consisting of a large number of people in a reasonably controlled homogenous environment, they are at high risk of developing acute upper respiratory infections during the six-week training period. Since medical care is uniformly provided to all trainees at nearby military medical facilities, access to medical records is enhanced. The natural division of trainees into groups which receive only limited outside interaction, provides an excellent setting for testing interventions such as the one addressed in this study.

3. Questionnaire Testing

Prior to beginning the study, a questionnaire was developed to ascertain information on trainee reported acute upper respiratory infection episodes, medical care seeking behavior, and handwipe use. Using recruits assigned to Medical Hold, the questionnaire was tested for reliability. Additional validity testing was accomplished later using the results from flights enrolled in the study.

Copies of the original draft of the questionnaire were presented to eighteen Medical Hold recruits. Each question was addressed separately by the proctor. Trainees were instructed to answer all questions to the best of their knowledge without additional instruction. After the completion of all questions, the proctor readdressed each question, asked the recruit if he understood the question and requested comments on any part of the question the trainee felt was ambiguous. Using recruit inputs, the questionnaire was edited to improve syntax and clarity.

The edited questionnaire was administered to twenty-two additional Medical Hold recruits in a self-administered fashion with a proctor present. Answers to the edited version were recorded using computer scantron sheets. The scantron sheets are similar to those used in routine basic training performance testing and recruits are familiar with their format. After completing the questionnaire, recruits were asked to comment on ambiguous questions.

The scantron sheets were later analyzed to identify illogical answers. An example of an illogical answer would be for a recruit to first respond that he did not get a cold during basic training and later record that he caught a cold during the second week of

training. Recruits recording illogical answers were interviewed individually. They were asked to explain their answers and provide comments on question improvement. Based on the results of these interviews the questionnaire was reedited.

Using a self-administered method with proctor and scantron sheets, the reedited questionnaire was given to 28 additional Medical Hold recruits. The results were reanalyzed for inconsistent and illogical answers. Ten days later the same questionnaire was readministered in the same manner to the 28 recruits. The results were compared for test-retest reliability[66].

Validity testing was conducted on three questions[67]. Using the second administration of the questionnaire, the results of questions regarding medical care seeking behavior were compared to medical record information. A final model of the questionnaire was approved for use based on the validity and reliability testing.

4. Phase I-Glove Juice Test

Forty Medical Hold recruits were randomly assigned to participate in a laboratory based test investigating the bactericidal properties of four hand-cleaning regimes. A modified version of the glove juice test[68] was chosen as the method to compare the four hand-cleaning regimes and determine their relative efficacy. The glove juice test is an FDA approved technique used extensively by surgical investigators. It provides a method of quantifying bacterial hand flora from the entire hand surface. The resulting hand counts of colony forming units provided an accurate and standardized method for making comparisons between the hand-washing regimes.

Volunteering recruits were excluded from the test if they were taking antibiotic medications, were assigned to work which would excessively contaminate their hands (cleaning latrines or emptying garbage bins), were unable to complete all parts of the test, or were unwilling to follow the prescribed hand-washing regime.

Each consenting volunteer was asked to submit to specimen collections from each of his or her hands on five separate occasions in a one week period. The first two specimens, collected on Friday and the following Monday provided baseline bacterial colony hand count information on each subject. Immediately following the second baseline specimen collection, the subject was randomly assigned to one of the hand-cleaning regimes. The hand-cleaning regime was initiated immediately and a second specimen was collected after one hour. Additional specimens were collected on Wednesday and Friday of the same week. All specimens collection were made at approximately the same time of day with the exception of the second Monday collection which by design was one hour following initial administration of the assigned hand-cleaning method.

As outlined in Appendix 2, the glove juice test consisted of placing nonpowdered sterilized latex surgical gloves on the subject's hands and filling the gloves with a prescribed amount of a solution designed to promote bacterial growth. After a specified contact time while the hand was gently massaged, the glove was removed and the solution transferred to a sterile container for transport. At the laboratory the solution was diluted ten and 100 fold. A small amount of the diluted solution (0.5 ml) was inoculated on a 5 percent sheep blood agar plate. The plate was aerobically incubated at 32 degrees

centigrade for 48 hours before colony counts were accomplished. Bacterial isolates were identified using standard laboratory methods.

To ensure an equal number of subjects in each arm of the trial, random assignment was made using four die. Each of the twenty-four possible order permutations of assignment for four subjects was given a number. The subjects were ordered based on the last four digits of their social security number and the four die were caste. Based on the sum of the die, the appropriate permutation was selected and the subject assigned. This process was repeated after each group of four subjects.

The hand-cleaning regimes tested consisted of the following. Regime one required of the use of handwipes containing 0.5% PCMX and 40% alcohol. Regime two provided for the use of the same handwipes plus the use of a soap containing triclosan. Regime three prescribed the use of a handwipe containing lemon juice and water. Regime four consisted of continuing to follow normal hygiene practices. Those assigned to regimes one, two and three were instructed to use their handwipes and soap four times daily at times associated with meals and bedtime. Subjects assigned to regime four were instructed on the importance on continuing their normal hygiene practices throughout the study period.

5. Phase II-Field Trial

Fifty flights, consisting of 2650 recruits comprised the second phase of the study. The recruits entered the trial during medical processing on Thursday or Friday prior to beginning formal training. This period, consisting of the two aforementioned days and subsequent weekend days, is referred to as Week Zero. After receiving a briefing on the

study and providing informed consent, the trainees were asked to submit to the collection of an oropharyngeal specimen. Each subject was provided with a package containing one week supply of handwipes and briefed on their use. Trainees were instructed to use the handwipes four times daily; once after each meal and once prior to bedtime.

On the Friday at the end of the first week of training, during medical processing, trainees were provided with an additional one week supply of handwipes and the instructions on handwipe use were repeated. Each subsequent week, handwipes were delivered to the trainee's squadron for distribution. Contact was made with the recruits' training instructor to reinforce the importance of compliance.

Rather than individual allocation to either of the two study treatment arms, random assignment was made by flight with all consenting flight members receiving the same intervention. To ensure an equal number of flights in each arm of the study, random assignment consisted of flipping a coin (heads treatment, tails placebo). Using two flights of the same sex entering training during the same day, the first flight was assigned to one treatment arm and second flight the other. Each flight had a brother flight assigned to the same squadron which entered training the same day. Since the brother flight was paired with the initial randomly assigned flight, matched flights were of the same sex, from the same squadron and entered training on the same day.

The study consisted of two treatment arms. Flights were either assigned to use individual wrapped handwipes containing 0.5% PCMX and 40% alcohol with an aloe based emollient (referred to as the treatment group) or handwipes containing water and lemon juice (referred to as the placebo group). The members of all flights, regardless of

treatment assignment, received the same instructions on handwipe use prior to treatment assignment. Handwipes were packaged in color-coded individual containers as depicted in Appendix three. Recruits and health care providers responsible for administering medical service were blinded to the type of handwipe assigned.

During the last week of training for each flight, a second oropharyngeal specimens were collected from each consenting flight member and questionnaires administered. The questionnaire was self-administered with a proctor present to address specific questions. Answers were recorded on scantron sheets.

The medical records of all trainees who sought medical care during the study period were reviewed. Trainees with medical complaints normally report to sick-call at the medical aid stations located within or in close proximity to their squadron. Each aid station maintains a daily log of with the name, social security number and flight assignment of each trainee reporting to sick-call. Using these logs to identify those seen, the medical records of each trainee were reviewed nightly by the investigator. Specific information obtained and recorded from the medical record review included the patient's diagnosis, the presence of pharyngitis signs or symptoms, and whether a throat culture was ordered. In addition to medical air station sick-call logs, emergency room logs, primary care clinic logs and hospital admissions logs were reviewed daily to identify all trainees seeking medical care.

Laboratory Techniques

The posterior pharynx and tonsils or tonsilar fossae of each trainee was swabbed with a cotton tipped swab. Approximately 98 percent of all specimens were obtained by

the same experienced individual using a standardized technique. Specimens were immediately inoculated onto 5 percent sheep blood agar plates. After all daily collections were made, the blood agar plates were transported to the laboratory for further processing. Each plate was further streaked to spread the inoculate over the entire plate surface and aid in colony differentiation. After aerobic incubation for 24 hours at 32 degrees centigrade, the blood agar plates were read for beta-hemolysis and colonial morphology. Suspicious colonies were restreaked for isolation on blood agar plates and a 0.04 unit bacitracin disc applied. After another 24-hour incubation period, isolates displaying any zone of inhibition were confirmed as *Streptococcus pyogenes* by latex agglutination for detection of specific group A polysaccharide. All Group A beta-hemolytic *S. pyogenes* isolates were saved by freezing in skim milk at -70 degrees centigrade[69].

6. Data Analysis:

Phase I-Glove Juice Test:

During phase I of the study, colony forming units served as a single endpoint for comparison between hand-cleaning regimes. Using the colony counts for a 1 to 100 dilution of the glove juice sampling solution, the total number of colony forming units per hand sample were calculated. Colony forming unit counts from both hands at each sampling period were averaged.

The first and second baseline samples from each subject were compared using paired t-test methodology[70]. Colony forming units counts from the third post intervention sample were subtracted from the average of the two baseline samples for each recruit.

This statistic formed the unit used in comparing hand-cleaning regimes using student t-test methodology[71]. Each hand-cleaning regime was compared to the other three regimes. A total of six such t-tests were accomplished. Since these tests were considered in the study design, no multiple testing corrections were included[72].

Gender was considered as a possible confounder to this analysis. Since subjects in each hand-cleaning regime were not matched for gender, multiple linear regression methodology[71], while controlling for gender, was applied to the above referenced endpoint.

Phase II-Field Study:

Because randomization was accomplished by flight rather than by individual, there is a loss of power over that realized through a subject-based analysis. From data collected over the past year at Lackland Air Force Base, the acute upper respiratory infection rate was estimated at 13.6 ($\pm$0.74) initial medical visits per 100 recruits. Based on this estimate and a target of a 45 percent reduction in sick-call visits with $\alpha = .05$ and $\beta = .10$, a sample size of 25 flights per treatment arm was calculated.

Significance testing for phase II was conducted using permutation test methodology[73]. The use of standard parametric analytical techniques, using the individual as the unit of analysis, would have produced greatly overestimated results since flights rather than individuals were randomized to either treatment or placebo handwipes and randomization was performed within flight pairs. To accomplish the permutation test on a specific endpoint, the sum of the 25 pairwise differences between treatment and placebo handwipe flights was calculated for 1,000 equally likely ways the 25 pairs could

have been assigned to handwipe type[74]. Under the hypothesis of no effect on outcome due to handwipe assignment, the distribution of the results from these 1,000 permutations should be normally distributed with a median result of zero[73]. The rank of the observed result from the study among the 1,000 permuted endpoints provides the significance level. A two sided permutation test was specified in the design phase of the study for all endpoints.

Endpoints to which permutation methodology was applied consisted of the following:

a. The incidence of acute upper respiratory infection as determined by medical record review. The percentage of recruits with an initial sick-call visit for an acute upper respiratory infection in a flight using antimicrobial handwipes was compared to the percentage of recruits with an initial sick-call visit for acute upper respiratory infection within the paired flight using placebo handwipes. The difference in these percentages (treatment group minus placebo group) was calculated for each flight pair.

b. The same comparisons were made using initial visits for sore throat as determined by medical record review.

c. Questionnaire obtained data were addressed similarly for statistics such as percentage reporting colds without sore throats, colds with sore throats, sore throats alone, reports of seeking medical care and frequency of handwipe use.

d. Demographic data such as age, race, and residence prior to entering basic training were similarly analyzed.

e. Within each flight, the proportion of recruits with a positive throat culture for GABS at the beginning of training was subtracted from that proportion with positive

cultures at the end of training. Differences in this change in GABS prevalence between treatment and placebo flights were calculated for each flight pair.

Data from individual trainees were analyzed under the constructs of 'intent to treat' methods[75]. In other words, recruits who recycled to other flights because they failed portions of their basic military training were considered as part of their originally assigned flight regardless of reassignment. Additionally, all recruits sent to Medical Hold were treated as though they had finished study participation regardless of whether they were returned to duty or separated from military service. Collection of sick-call data was terminiated at the time of assignment to the Medical Hold squadrom. Throat cultures specimens were collected and questionnaires completed while the recruits were in Mecical Hold status; usually within two days of this assignment.

Chapter III

Results

1. Questionnaire Reliability and Validity

Twenty-eight recruit members of the Medical Hold squadron completed the questionnaire shown in Appendix 4 on two occasions ten days apart. The answers to sixteen of the eighteen questions specified on the questionnaire were analyzed for test-retest reliability. Two questions which dealt with the frequency of handwipe use were not considered for test-retest reliability analysis since questionnaire testing occurred prior to beginning the study and handwipes were not available to the participating subjects. Using a self-administered method, the same proctor provided the questionnaire to the recruits on both occasions. In both instances, recruits were told to read the opening paragraph on the questionnaire form prior to answering any questions and to use the answer sheet provided. While the proctor was available to answer questions during both sessions, he was not approached to provide further instruction either time.

Test-retest analysis was accomplished by deriving a kappa statistic for each question under study. Kappa statistics ranged from 0.17 to 0.99 with the lowest test-retest agreement seen in questions related to the presence and severity of a sore throat on the day the questionnaire was administered. The highest kappa statistic was derived from the question requesting race information. Reliability was higher among questions related to whether a recruit acquired an acute upper respiratory infection than for frequency of illness episodes (Table 3).

Table 3. Kappa statistics for test-retest analysis of study questionnaire[1,2]

Question	Kappa
Cold with sore throat reported	.91
Frequency of cold with sore throat episodes	.68
Sought medical care for cold with sore throat	.75
Cold without sore throat reported	.83
Frequency of cold without sore throat episodes	.51
Sought medical care for cold without sore throat	.61
Sore throat without cold reported	.58
Frequency of sore throat episodes	.55
Sought medical care for sore throat	.67
Week of training when first cold acquired	.73
Week of training when first sore throat acquired	.77
Current sore throat status	.18
Severity of current sore throat	.16
Cold or sore throat at beginning of training	.67
Reported race	.99
Dry or sore hands during training	.67

1. U.S. Air Force recruits assigned to Medical Hold squadron(n = 28)
2. Questionnaire administered twice at ten day intervals

Validity testing was conducted on three questions which requested information on medical care seeking behavior. The answers elicited during the second administration of the questionnaire were compared to those obtained by medical record review. For all subjects, the medical record was reviewed by the same investigator. Using the subject's medical records as the gold standard, sensitivity and specificity percentages were derived. Sensitivity ranged from 100 to 66.7 percent. The questions which asked whether the subject sought medical care for a sore throat achieved the lowest sensitivity, however this finding may reflect the small numbers of such cases. Specificity ranged from 92 to 86.4 percent with lowest specificity associated with questions relating to the seeking of medical care when the subject suffered from a cold without a sore throat (Table 4).

2. Phase I-Glove Juice Test

Forty of the 92 recruit volunteers for the glove juice test were accepted into the study and completed all parts of the trial. Of those eliminated, 46 were unable to complete the entire trial due to planned military separation during the study period. Four recruits were eliminated due to details involving the cleaning of latrines and two trainees were taking antibiotics at the time of the trial. The subjects consisted of 24 females and 16 males between 18 and 23 years of age. All subjects reported using the handwipes assigned as directed. In one instance, handwipes were reissued due to the recruit misplacing the original issue.

After averaging the bacterial handcount from each recruit, the two baseline samples were compared. Bacterial handcounts ranged from 30,000 to 6,250,000 colony forming units with a mean count of 1.4 and 1.1 million units respectively for the two

Table 4. Validity testing of three questionnaire answers showing sensitivity specificity and kappa statistics[1,2]

Medical care sought for cold with sore throat	Sensitivity	100%
	Specificity	86.4%
	Kappa	73.1
Medical care sought for cold without sore throat	Sensitivity	100%
	Specificity	90%
	Kappa	83.7
Medical Care sought for sore throat without cold	Sensitivity	66.7%
	Specificity	92%
	Kappa	51.1%

1. U.S. Air Force recruits assigned to Medical Hold Squadron (n = 28)

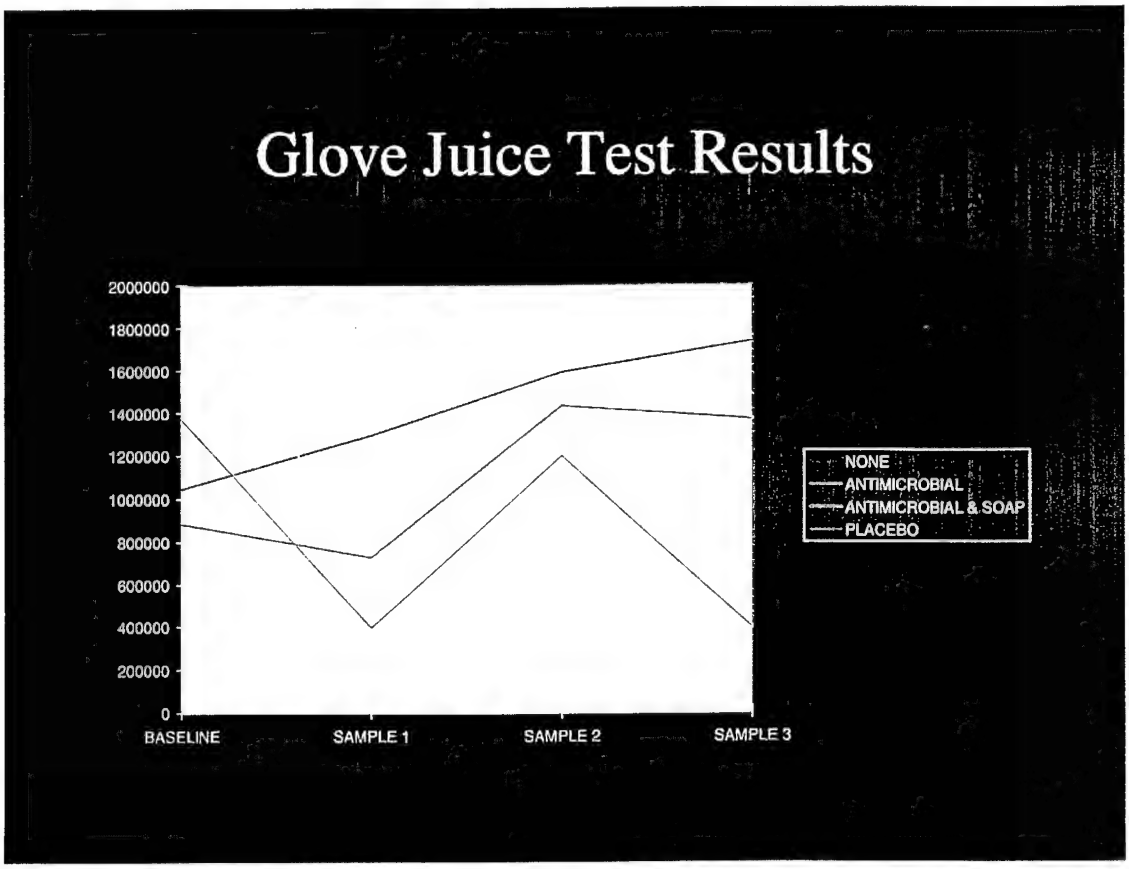
2. Medical visit information obtained from medical record review considered gold standard.

samples collected. Results of paired t-tests comparing first and second baseline samples showed no significant differences (P=0.43) (Table 5). Differences were found between two of the four intervention groups (antimicrobial handwipes and placebo handwipes) (P=0.016) with respect to the average of the two baseline hand colony counts.

At one hour after first use, those randomized to receive antimicrobial treated handwipes and soap containing triclosan showed a 71.4 percent decrease in colony counts. Those using the antimicrobial handwipes alone experienced a 57.9 percent decrease. Among those using placebo handwipes, the reduction in colony handcounts was much lower at 11.1 percent. Recruits assigned to no treatment showed an increase (14.2%) in colony numbers (Figure 1).

At the time of the second post intervention sample collection, hand colony counts had uniformly risen from the time of the previous collection two days earlier. Among those using antimicrobial handwipes and triclosan soap, colony counts remained below baseline levels showing a 14% decrease. Those using antimicrobial handwipes alone maintained much lower bacterial levels with a 52% decrease from baseline levels. Among those using placebo handwipes, colony handcounts had risen above baseline levels by 64.7 percent. Handcounts had also risen to 142% of baseline levels for those assigned to the no treatment group. By the end of the study period, those using antimicrobial handwipes had experienced substantial decreases in hand colony counts. Decreases of 71.4 and 78.9 percent respectively were seem among those using antimicrobial handwipes with and without soap containing triclosan. Among those not using antimicrobial handwipes hand

Figure 1. Glove juice test results measuring colony forming units (CFU) at sampling intervals.



U.S. Air Force recruits assigned to Medical Hold squadron (n=40)

colony counts remained above baseline levels. The difference between baseline average and final sample hand colony counts were used to compare the four intervention groups. There was no significant difference found between the two groups assigned to use antimicrobial handwipes at the 0.05 P-value level. Similarly, no differences were found between the two groups that did not use antimicrobial handwipes. Highly significant differences ($P < .01$) were noted, however, when groups using antimicrobial handwipes were compared to those not using treated handwipes (Table 5). After adjusting for sex and average baseline hand colony count these differences remained highly significant.

Organisms isolated before and after intervention were identified. The majority of bacteria cultures before disinfection were coagulase negative staphylococci. Coagulase positive staphylococci, *Bacillus spp, Micrococcus spp, Corynebacterium spp,* and undetermined gram negative rods were also isolated in small numbers. After the use of the antimicrobial handwipes and triclosan containing soap, coagulase negative staphylococci were found exclusively. Among those using not using antimicrobial handwipes, in addition to coagulase negative staphylococci, Staphylococcus aureus and gram negative rods for identified. *Streptococcus spp.* were not isolated from any of the samples collected.

3. Phase II-Field Trial

Study Population

Data on the study population participating in the field trial was derived from flight roster information and the questionnaires completed by the recruits. Of the 2682 eligible recruits, 2650 trainees from 12 female and 38 male flights participated in the study.

Table 5. Glove juice test results comparing hand colony forming unit counts among and between groups[1].

Within Groups Baseline sample comparisons (paired t-test).

Sample	Mean Count	P-value
Baseline 1	1,400,000	0.52
Baseline 2	1,202,312	

Between Groups Change in hand colony counts (average baseline minus final sample). Independent t-test with unequal variances.

Group Comparison[2]	Mean Difference	P-value
Group 1 vs. Group 2	1,995,625	.001
Group 1 vs. Group 3	536,000	.162
Group 1 vs. Group 4	2,198,500	.001
Group 2 vs. Group 3	-1,459,625	.001
Group 2 vs. Group 4	202,875	.632
Group 3 vs. Group 4	1,662,500	.003

Between Groups Change in hand colony counts (average baseline minus final sample). Multiple linear regression controlling for gender and average baseline hand colony count.

Group Comparison	P-value
Group 1 vs. Group 2	.001
Group 1 vs. Group 3	.379
Group 1 vs. Group 4	.001
Group 2 vs. Group 3	.001
Group 2 vs. Group 4	.524
Group 3 vs. Group 4	.001

1. U.S. Air Force recruits assigned to Medical Hold squadron

2. Group 1 = Antimicrobial handwipes
   Group 2 = Placebo handwipes
   Group 3 = Antimicrobial handwipes and triclosan containing soap
   Group 4 = No change in normal hygiene practices

Twenty-five flights (6 female and 19 male) were randomly assigned to each arm of the trial. A total of 2493 recruits (94.1%) completed all parts of the study. Those trainees (n=157, 5.9%) for which all data was not obtained failed to complete the questionnaire at the end of the study and to submit a second throat culture. The majority of those not completing all parts of the study (58.6%) refused participation during the occasion of questionnaire completion and throat culture collection. Thirty-six percent were unavailable for follow-up due to early dismissal from basic training either due to separation from military service or early graduation (Table 6). The race, age, and sex of those lost to follow-up did not differ markedly from the study population.

Subjects ranged in age from 17.6 to 28.4 years with a mean age of 20.7 years. Nearly half (48.9%) were under twenty years of age when they started basic training. The majority were white (68.6%) with blacks making up the second largest racial group. Although recruits enter basic training from every state in the nation as well as United States territories, the majority (32.2%) came from western states. A small percentage of recruits (10%) reported suffering from colds or sore throats when they received medical processing at the beginning of basic training. No difference in age, race, gender, region of prior residence, or presence of acute upper respiratory infection at the beginning of training was found associated with assignment of handwipe type (Table 7).

Throat Culture Results

Approximately ten percent of the oropharyngeal specimens collected prior to the beginning of basic training were found positive for Group A beta-hemolytic *Streptococcus pyogenes.* Those flights assigned to use antimicrobial handwipes contained slightly more

Table 6 Phase II-Field Study. Eligible and participating subjects including information on those lost to follow-up.[1]

Subjects	Number
Eligible	2682
Male	2040
Female	642
Consenting	2650
Antimicrobial Handwipe Group	1330
Male	1005
Female	325
Placebo Handwipe Group	1320
Male	1003
Female	317
Completed Entire Study	2493
Antimicrobial Handwipe Group	1258
Male	951
Female	307
Placebo Handwipe Group	1235
Male	941
Female	294
Lost to Follow-up	157
Refused Second Throat Culture and Questionnaire	92
Early Graduation	29
Early or Rapid Separation	28
Unavailable (Jail, AWOL, Special Duty)	8

[1] U.S. Air Force Recruits assigned to Lackland Air Force Base, TX

GABS positive members than those assigned placebo handwipes (1.38 vs. 0.78% respectively). This difference was not significant (P = 0.20). At the end of training when the second specimen was collected, the proportion of GABS positive recruits in flights using antimicrobial handwipes had remained relatively stable at 1.22 percent (12% decrease from day 0). Among those using placebo handwipes, however, the rate of GABS positive recruits had increased to 3.02 percent (287% increase from day 0) (Figure 2). The difference between antimicrobial and placebo assigned flights with respect to their change in GABS positive throat culture prevalence was highly significant (P = 0.016).

Sick-call Results

Among the 2650 recruits participating in the study, 1402 initial sick-call visits were experienced (52.9 sick-call visits/100 trainees). Acute upper respiratory infection accounted for 37.8% of the total initial sick-call visits. Flights using antimicrobial handwipes experienced a slightly lower sick-call visit rate when compared to flights using placebo handwipes. This reduction was not, however, statistically significant (P = 0.317). With respect to sick-call visits for acute upper respiratory infection, flights using antimicrobial handwipes experienced a pronounced 32.7 percent reduction in visits when compared to flights using placebo handwipes (P=0.021). The rate of reduction due to antimicrobial handwipes was more striking (40.0%) when sick-call visits for sore throat were compared (P=0.009). Sick-call visits with a diagnosis of strep throat (GABS positive by laboratory analysis) were reduced ten fold for antimicrobial handwipe using flights (P =0.041) (Table 8). Figure three depicts the differences in flight sick-call rates associated with handwipe use.

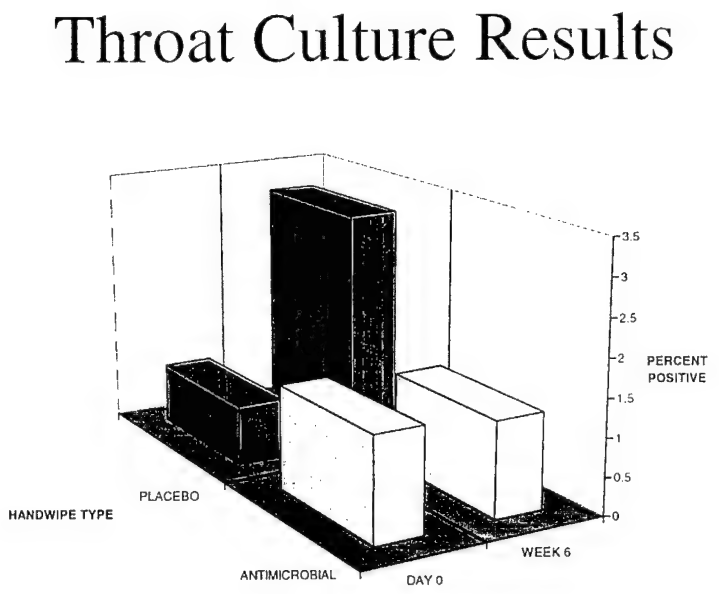
Table 7. Demographic information on U.S. Air Force recruits participating in Phase II-Field Study[1]

	Antimicrobial	Placebo
Flights		
Male	19	19
Female	6	6
Consenting Subjects	1330	1320
Gender		
Male	1005	1003
Female	325	317
Race (%)		
White	68.0	69.2
Black	17.2	18.2
Hispanic	7.9	7.5
Other	6.9	5.1
Age in Years (Mean)	20.7	20.7
Age Group in Years (%)		
<20	48.5	49.8
20 to 22	38.9	36.5
23+	12.6	13.7
Region of Prior Residence		
East	16.8	17.2
Central	23.0	23.3
South	25.9	25.7
West	32.2	32.0
Other[2]	2.1	1.8
Acute upper respiratory infection when Training Began (Percent of Flight Members)		
Yes	9.8	10.2

1. U.S. Air Force recruits assigned to Lackland AFB, TX.

2. Other = Alaska, Hawaii, U.S. territories or foreign countries.

Figure 2. Results of throat culture analysis from specimens collected on training day 0 and the last training week. Results are displayed by handwipe type assigned to flight.



U.S. Air Force military recruits assigned to Lackland Air Force Base Texas (n=2650).

Under current preventive medical guidelines at Lackland Air Force Base, flights receive mass treatment with benzathine penicillin when more than three recruit members contract GABS pharyngitis[76]. This procedure is designed to prevent further cases in the flight and protect members from untoward complications associated with untreated disease. During the period of this study, three flights reached the GABS case threshold and received mass prophylactic treatment. Of note is the fact that all three flights were assigned to placebo handwipes.

Questionnaire Results

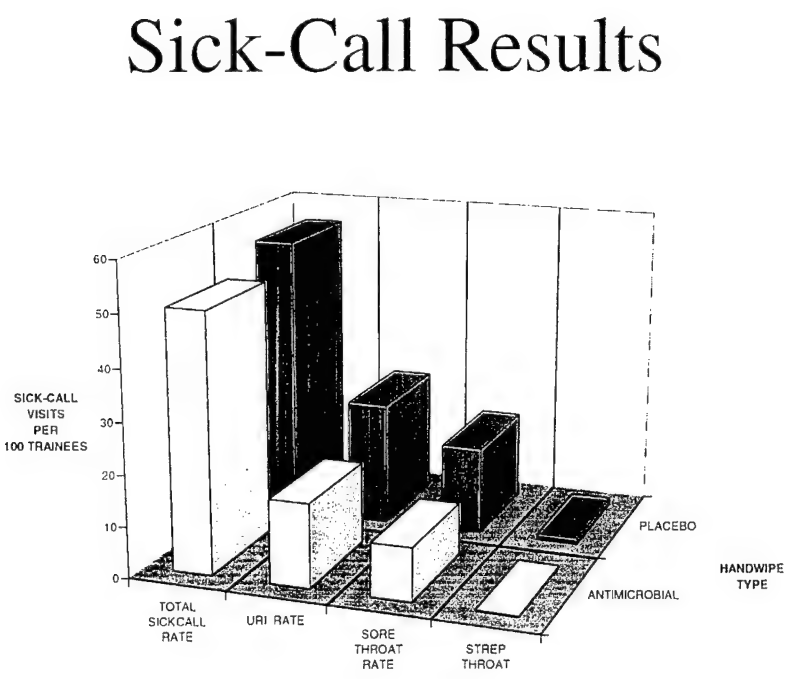
A total of 2493 recruits completed the questionnaire. Approximately 84 percent reported coming down with a cold during the training period. Ninety percent of the trainees reported suffering from a cold, a sore throat, or both during the six weeks of basic training.. Thirty four percent reported suffering from a sore throat alone. Among those contracting a cold, 21 percent reported that they initially became ill during the first seven days of training. For those reporting sore throats, 34.6 percent first contracted the illnesses in the initial training week. Approximately 10 percent reported they were ill with a cold or sore throat when they started basic training and 16.3% reported having a sore throat at the time of questionnaire completion. With respect to handwipe type, no differences between flights were detected in the percent who reported contracting colds, sore throats, or both (Table 9). Among recruits who suffered a cold with or without a sore throat, those using placebo handwipes were 20 to 30 percent more likely to seek medical care. This difference in medical care seeking behavior did not, however reach statistical significance at the 0.05 level ($P = 0.129$ and 0.062 respectively) (Table 10).

Table 8. Initial sick-call visit rate with comparisons between antimicrobial and placebo assigned handwipe flight pairs[1,2].

Initial sick-call visit type[3]	Antimicrobial Handwipes	Placebo Handwipes	P-value
Total sick-call	50.3	55.5	.317
Acute upper respiratory infection	16.2	24.1	.021
Sore throat	10.2	17.0	.009
Strep throat[4]	0.1	1.0	.041

1. U.S. Air Force recruits assigned to Lackland Air Force Base, TX
2. n = 2650 recruits, n = 50 flights
3. Sick-call visits per 100 recruit flight members Initial sick call visit is defined as the first medical visit associated with a specific condition. Follow-up and laboratory visits are excluded.
4. Strep throat is defined as Group A Beta-hemolytic Streptococcus pyogenes pharyngitis as determined by laboratory analysis.

Figure 3. Initial sick-call visit rate as measured by the number of visits per 100 recruits per flight. Comparisons made between flights assigned to antimicrobial and placebo handwipes.



Less than half (42.9%) the trainees reported using the provided handwipe three or more times daily and only slightly over half (56%) used them three or more days weekly. These findings indicate that handwipe use was considerably below the instructed level of four handwipes daily per recruit. The level of handwipe use was not associated with type of handwipe assigned. Stratification of each flight by level of handwipe use revealed that those among antimicrobial handwipe assigned flights who used fewer than five handwipes weekly showed a 32 percent reduction in initial sick-call visits for acute upper respiratory infection compared to their counterparts in placebo assigned flights. Among those using 15 or more handwipes each week, those in antimicrobial handwipe assigned flights were at 42 percent lower risk of acute upper respiratory infection, as measured by initial sick-call rates, than those who used the same number of handwipes in placebo assigned flights. (Table 11). Differences in initial sick-call rates between antimicrobial and placebo assigned flights reached significance for the high handwipe use strata ($P=0.042$).

Among those who attended sick-call for a sore throat, the level of handwipe use was found less dose dependent. The percentage of recruits with initial sick-call visits in the flight remained constant at approximately 10%, regardless of level of handwipe use, among those flights assigned to antimicrobial handwipes. For flights using placebo handwipes the percentage of initial sick-call visits for sore throat ranged from 44 to 55 percent with the high percentage among those using fewer than 5 handwipes weekly (Table 11). In spite of stratification and the resultant fewer recruits in each strata, the differences in sick-call rates for sore throat between antimicrobial and placebo assigned flights were significant for both the low and high handwipe use strata ($P < 0.05$).

Table 9. Results of questionnaire administered to recruits in study population with comparisons between flights assigned to antimicrobial and placebo handwipes[1,2].

Condition Reported[3]	Antimicrobial Handwipe	Placebo Handwipe	P-value
Acquiring:			
Cold with sore throat	65.0	64.9	.960
Two or more times	33.0	31.8	.548
Cold without sore throat	52.8	51.8	.764
Two or more times	22.9	22.8	.920
Sore throat without cold	36.1	33.1	.139
Two or more times	19.5	17.1	.186
Any cold	84.8	83.5	.453
Any cold or sore throat	90.6	89.6	.395
Ill with a cold or sore throat at beginning of training	9.8	10.2	.764
Ill with a sore throat at time of questionnaire completion	16.8	15.7	.549

1. U.S. Air Force recruits assigned to Lackland Air Force Base, TX.
2. n = 2493 subjects, n = 50 flights.
3. Percentage of flight members.

Table 10. Results of questionnaire administered to recruits in study population who reported acquiring a cold or sore throat. Comparisons made between flights assigned to antimicrobial and placebo handwipes[1,2].

Condition Reported[3]	Antimicrobial Handwipe	Placebo Handwipe	P-value
Acquiring:			
Cold with sore throat			
Sought medical care	19.2	24.1	.129
Cold without sore throat			
Sought medical care	7.3	10.4	.062
Sore throat without cold			
Sought medical care	7.2	6.0	.688
Cold during or before first week of training	22.8	19.9	.312
Sore throat during or before first week of training	36.9	32.3	.208

1. U.S. Air Force recruits assigned to Lackland Air Force Base, TX.
2. n = 2493 subjects, n = 50 flights.
3. Percentage of flight members.

Because the handwipes containing PCMX and alcohol could potentially result in skin irritation, hand dryness associated with handwipe use was also considered. While those who used the antimicrobial handwipes were at slightly higher risk (24.9 vs. 21.1%) of developing dry, red or sore hands, the difference was found not to be significant.

Table 11. Results of questionnaire administered to recruits in study population. Initial sick-call visit rates stratified by reported handwipe use. Comparisons made between flights assigned to antimicrobial and placebo handwipes[1,2].

Questionnaire Reported[3]	Antimicrobial Handwipe	Placebo Handwipe	P-value
Used handwipes 3+ times daily	42.7	43.0	.920
Used handwipes 3+ days weekly	55.1	56.7	.689
Dry, sore, red hands	24.9	21.1	.090
Sick-call rates[4]			
Low handwipe use (1 to 5 handwipes weekly)			
Sick-call visits for acute upper respiratory infection	17	25	.121
Sick-call visits for sore throat	10	22	.028
Moderate handwipe use (6-14 handwipes weekly			
Sick-call visits for acute upper respiratory infection	14	21	.162
Sick-call visits for sore throat	9	16	.100
High handwipes use (15+ handwipes weekly)			
Sick-call visits for acute upper respiratory infection	15	26	.042
Sick-call visits for sore throat	9	18	.023

1. U.S. Air Force recruits assigned to Lackland Air Force Base, TX.
2. n = 2493 subjects, n = 50 flights.
3. Percentage of flight members.
4. Initial sick-call visits per 100 flight members.

Chapter IV

Discussion

1. Study Limitations

Several potential limitations should be considered in the interpretation of the study findings. For the glove juice test in Phase I, these include: the length of the study period, the selection of Medical Hold recruits as subjects, and the appropriateness of the glove juice test as a decision making model for Phase II of the study. For the field trial, the limitations include: the lack of a second (no handwipe) placebo group, potential differences among separating flight member's time at risk, differential effects of ventilation between flights, possible incomplete ascertainment of sick-call cases, the loss of subjects to follow-up, the lack of a recruit performance measure and the completeness of blinding subjects and health care providers to handwipe type. Lastly the issue of testing only one antimicrobial handwipe formulation must be considered.

Phase I-Glove Juice Test

Length of the study period:

Based on prior knowledge [56,77], we had predicted that a one week study period would have been sufficient to note differences between the hand-cleaning regimes. While these differences were in fact seen during the study, the variability in hand colony counts at the post intervention sampling times led to some surprising findings and speculation that a longer study interval was needed.

Glove juice specimens were collected from both hands of each subject on five separate occasions over a period of one week. Those assigned to hand-cleaning regimes

containing antimicrobial handwipes experienced a significant drop in hand colony forming units over the study period. However, a large proportion of the decline occurred between the second and third post intervention collections. In fact, all groups experienced a rise in hand colony counts between the first and second collections after randomization and application of the hand-cleaning regime. This increase is likely due to the dramatic effect of the hand-cleaning regimes over the short interval between the initial application of the hand-cleaning regime and the collection of the specimen (1 hour). While subjects waited quietly for the collection of their specimens after the initial application, collection of the second post intervention sample two days later allowed time for subjects to contaminate their hands while going about their daily routine.

We speculate that the overall reduction in hand colony counts associated with the use of antimicrobial handwipes and triclosan containing soap is due to the cumulative effect of exposure to the disinfectants over time. However, because the period of study ended at one week, just when large reductions in hand colony counts were noted, we have no way of determining if the decreasing pattern of hand colony counts would continue. It is possible that a rebounding of hand colony counts could occur during the second week of use. If such an increase were to take place evidence supporting the use of antimicrobial handwipes could be weakened. Conversely, we noted a steady, but statistically insignificant, increase in hand colony counts among those assigned to continue normal hygiene practices. Because the study was terminated as planned at the end of one week, there is no way to determine if this increase would continue, level out or fall back to

background levels. In any case, the glove juice test would have been better supported by a longer study.

The selection of Medical Hold recruits as subjects:

As stated earlier, recruits in the Medical Hold squadron come from the general population of recruits attending basic military training. As such, they should be representative of the basic training population as a whole. Although there are slightly more females in Medical Hold than in the basic training general population, the recruits in Medical Hold are representative with respect to age, level of education, region of prior residence, type of housing and other characteristics. One important area where they differ, however, is in the type of daily activities conducted as part of training. Because recruits are transferred to Medical Hold pending medical and administrative actions, their work day is much different from most trainees. While recruits in training are undergoing intensive physical training and educational instruction, recruits in Medical Hold spend their days attending medical appointments or conducting work details involving minimal exertion. Recruits in training attend classes in lecture rooms that hold 50 to 100 trainees. Medical Hold trainees do not attend any formal classes and meet in groups of usually 10 trainees or less.

These differences in daily activity translate into differences in exposure to potentially pathogenic bacteria and environmental contaminates. The level of exposure to environmental contaminates is likely much lower for Medical Hold recruits. Additionally, because they do not assemble in large groups, the probability of having one's hands inoculated with pathogenic bacteria from another person is lower. Finally, because the

Medical Hold trainees do not exert themselves physically to the extent of those recruits in training, they do not perspire as heavily. Perspiration may act to remove some pathogenic bacteria from the hands and thereby afford a level of protection.

Because of the differences in daily activities, Medical Hold recruits may not be entirely representative of the general population with respect to the results of the glove juice test. Medical Hold recruits may have lower background handcount levels. The hand-cleaning regimes may also have a greater effect among Medical Hold recruits than their recruit in training counterparts due to a lower level of bacterial contamination and less dilution due to perspiration.

Although it would have been optimal to use recruits in training for the glove juice test portion of this study, it was logistically impossible to put together such a group given the constraints of the training schedule. As such, caution should be taken in referring the results of the glove juice test to the general population of recruits in training. The basic premise for conducting the test, however, should be kept in mind when considering the glove juice test findings.

The appropriateness of the glove juice test as a decision making model:

The results of the test were expected to provide information needed to make decisions regarding the second part of the study; the field trial. There were concerns about whether the addition of a soap product containing triclosan would sufficiently improve hand cleanliness and contribute to lower acute upper respiratory infection rates. If so proven, such an arm could be added to the field study. Additionally there were concerns as to whether a handwipe containing lemon juice and water could serve as a

placebo. If bacterial handcounts were lowered compared to the no treatment group in the glove juice test, there would be evidence that the water and lemon juice placebo had a germicidal or mechanical cleaning effect. Such a finding would provide evidence for the need of a no-treatment arm in the field trial.

While the findings of the glove juice test showed a significant reduction in bacterial hand colony counts associated with exposure to antimicrobial handwipes and that the addition of triclosan soap provided no additional reductions, the appropriateness of the test as a decision making instrument is questionable. The glove juice test as applied in this study measured reductions in the normal hand bacterial flora. The process of preparing hands for specimen collection required that they be washed with a non-antimicrobial soap and rinsed with sterile water. This procedure effectively removed large numbers of transient bacteria from the hands. Of note is the fact that no specimens contained streptococcal bacteria and only a few specimens with gram negative rods were collected.

The bacteria and viruses capable of causing acute upper respiratory infection by direct contact are not part of normal hand flora. As transient contaminates of the hands, they were likely effectively removed during the hand preparation procedures of the glove juice test. Therefore, the glove juice test as applied was not the optimum test for the effectiveness of the hand-cleaning regimes in this study. It is possible that all hand-cleaning regimes, except the 'no treatment' regime, could have worked equally well at removing transient pathogens. That possibility, however, was not effectively tested.

A modification to the glove juice test, as conducted in this study, would have been to eliminate the use of soap washing and sterile water rinses prior to specimen collection.

While this would have been possible and may have led to better qualitative results, wide variations in hand colony counts could have made quantitative analysis of results untenable.

Based on the study design, the glove juice test results justified the decision to employ only two arms to the field trial. While this decision lead to positive findings, the rationale for making the decision can be questioned.

Phase II-Field Trial

The lack of a second (no handwipe) placebo group:

As designed, the handwipe field trial contained two intervention arms; antimicrobial handwipes and placebo handwipes. While results of the study were positive with respect to reductions in sick-call visits and Group A beta-hemolytic *Streptococcus pyogenes* positive throat culture prevalence, it is possible the true measure of reduction was not realized. Consistent with the results of the glove juice test, handwipes containing lemon juice and water were assigned as a placebo. It is possible, however, that these placebo handwipes had some impact on the presence of pathogens on subject hands. Evidence of this possibility comes from anecdotal reports from basic training health care providers and training instructors. On several occasions, it was reported that the level of cold and sore throats were unusually low during the study period. This feeling was expressed repeatedly with respect to the streptococcal pharyngitis infection rate. Clouding this issue was the fact that only 1 percent of the incoming recruits were found positive for GABS on throat culture. This rate was well below those found in other studies of similar aged subjects[7,78,79].

Although the possibility exists that the placebo handwipes reduced direct contact transmission of upper respiratory pathogens, this effect was likely minimal. Any action by the placebo would have the result of attenuating the effects of the antimicrobial handwipes. As such, the true differences associated with antimicrobial handwipe use could be larger than those seen in the study.

The alternative of using a "no treatment" group in this study would not have been without problems. Because subjects were told of the study as part of providing informed consent, those not receiving handwipes would have been treated differently. It is likely that the act of instructing recruits on proper use of handwipes, in itself, had an effect. This effect would have been differentially applied to a theoretical 'no treatment' group and contribute to study bias; particularly with respect to questionnaire derived data.

Potential differences among separating flight member's time at risk

Recruits who separated from military service prior to completion of basic training contributed less time at risk than those who completed training. Even though the differences were, by definition, six weeks or less, given the short incubation period of upper respiratory infections, it is possible that this situation could affect study results. If separation from military service were associated with assigned handwipe type, results could be skewed. A review of flight rosters at the beginning and end of training, however, indicates no difference in the proportion of separating trainees with respect to handwipe assignment. Further, no differences among flights were noted in the average week of training for separating recruits. Although trainee sick-call visits were counted against the recruit's originally assigned flight in an "intent to treat" analysis, a subsequent review of

acute upper respiratory infection among those reassigned to the Medical Hold squadron prior to separation showed acute upper respiratory infection rates similar to those of recruits in training. As such, we do not believe there are significant differences among flights in the time at risk for separating airmen; nor do we believe this factor had an effect on study results.

Ventilation effects:

Ventilation has been shown to play an important role in the transmission of the pathogen associated with upper respiratory infection[80]. Since recruits spend a considerable amount of time in the squadron building, it would be conceivable that differences in ventilation between squadrons could effect the incidence of upper respiratory infection among assigned recruits. In fact, one squadron had higher rates of both upper respiratory infection and sore throats than all others. However, the resultant effect on this study was mitigated by the process of randomization and analysis. Since every flight randomized to receive antimicrobial handwipes was paired with a flight assigned to placebo handwipes from the same squadron, the impact of ventilation should have been effectively controlled. In nearly all cases, pair flights were housed on the same floor of the squadron building and therefore exposed to the same air handling system; further minimizing any differential effects associated with ventilation.

Possible incomplete ascertainment of sick-call cases:

Sick-call rates were determined through daily reviews of sick-call, emergency department and primary care treatment logs. The medical records of those seeking care on a given day were subsequently reviewed to confirm diagnosis and ascertain presenting

symptoms. On several occasions the medical records were not available immediately for review. On a few cases (n=11) it took several days to obtain the records for review. Additionally, just prior to basic training graduation, the recruit's medical records were transferred to a central processing station for shipment to their next duty location. While the number of recruits seeking care during this time when medical records were unavailable was small, it proved extremely difficult to obtain the data necessary to confirm diagnoses in those cases. It is possible that treatment information important to this study was missed by the record reviewer in those few cases. We feel, however, that any loss of medical information should be independent of flight assignment. Evidence supporting the fact that little data was lost came from concurrent reviews conducted by the base military public health department. Flight sick-call rates in this study were found identical to those reported during the public health review.

If such nondifferential loss of information resulted in missed sick-call visits, the resultant effect would attenuate any true differences between flights. As such, the positive differences in sick-call rates associated with antimicrobial handwipes are potentially greater than those seen in the study.

Loss of subjects to follow-up:

Approximately six percent of the subjects enrolled in the study were lost to complete follow-up. While these subjects were evenly distributed across all flights, such losses could potentially bias study results if those lost were different from the rest of the study population with respect to their acute respiratory disease risk. Those lost from the study did not complete the questionnaire at the end of the study and did not submit to a

second throat culture collection. However, sick-call visit information was collected on these recruits throughout the study period. The findings associated with sick-call visits did not suffer from any bias associated with the loss of these recruits to follow-up. Additionally, review of medical records for those not completing all parts of the study revealed neither an unusually high or low incidence of upper respiratory infection or sore throat compared to the flight members who completed the study. Based on these findings, we consider it unlikely that the loss of information on those recruits who did not complete the entire study contributed any significant bias to the study results.

Lack of a recruit performance measures:

Several endpoints of medical importance were tested in this study. However, a critical question to military leaders, the effect of acute upper respiratory infection on recruits performance, was not measured. It is conceivable that reducing either the number of severity of respiratory infections could improve their performance to the physical and mental challenges of basic training. Objective performance measures could exist in the form of written test scores and aerobic fitness reports. Unfortunately, these measures were not available during this study. Future studies should consider addressing performance issues.

Blinding subjects and health care providers:

The study design included blinding both subjects and health care providers to the flight assignment of handwipe type. The breaking of the blind could lead to differential results based on the health provider's or subject's personal beliefs regarding specific handwipe efficacy. Handwipe packets were identical in design with the exception of the

color of the lettering on the outside of the individual packets (Appendix 3). The chemical formulation applied to each handwipe type varied markedly which resulted in slight differences in odor. It would have possible for an astute recruit to tell the difference between handwipe types if each were available for his inspection. Since entire flights were randomized to receive one handwipe type, such comparisons between handwipe types would have been difficult. In spite of differences in smell, blindness was maintained by not informing the recruits or health care providers which formulation was considered the true antimicrobial product.

The endpoint most resistant to breaks in blindness was the throat culture results. The first throat culture specimen was collected prior to flight handwipes assignment. Further, it is highly unlikely that a recruit's knowledge of handwipe type could change the results of the second throat culture. Additionally, laboratory personnel were totally blinded to handwipe assignment and had no contact with recruits until the time of the second throat culture collection.

Sick-call visit information could be affected by breaks in blindness if the diagnosing health care providers were aware of recruit handwipe assignment and knew the color code. The health care providers most intimately involved with recruit medical care were medical aid station physician assistants. Post study interviews with those providers revealed that they were uniformly unaware of the coding system for the handwipes. In fact, two of the physician assistants asked to see the handwipes at the time of the interview because they had not previously been afforded the opportunity to inspect them. Based on these interviews, and the safeguards used during the study, we feel it is unlikely that

blindness was broken in the case of the health care providers. As such, sick-call visit information should be reasonably free of associated bias.

The endpoints most likely effected by a break in blindness are those related to the questionnaire. A recruit's knowledge of whether their flight received antimicrobial or placebo handwipes could influence his or her answers to the questions. While the safe-guards incorporated in the study design were considered adequate, possible breaks in blinding could not be entirely ruled out. In an effort to gain insight into the level of this potential problem, recruits were asked at the time of questionnaire completion to respond by raising their hands if they thought they got the "good handwipes or the fake ones". In none of the flights so questioned was there a unanimous consensus on handwipe assignment. Most flights were evenly divided in their response to the question. Only one flight responded with more than 60 percent of the flight members giving a common answer. In that flight, 65 percent of the recruits correctly answered that they had received placebo handwipes.

In spite of the above assurances that blindness was adequately maintained throughout the study, it is possible that the questionnaire results were influenced by the recruit's knowledge of handwipe type. Therfore, questionnaire results should be viewed with caution.

Testing antimicrobial handwipe formulations:

This study used addressed comparisons between placebo handwipes and a single formulation of antimicrobial handwipes. The antimicrobial formulation tested was selected because results of previous studies [41,51,53] and because the chemical used are

relatively free of serious side effects [53]. It is reasonable to assume that other antimicrobial agents could be delivered via handwipe vehicles. Additionally, the strength of the ingredients in the antimicrobial handwipes used in this study could be varied and tested. Due to the large number of recruits needed to conduct this study, it was nit considered feasible to test different types of antimicrobials. Additionally, since different antimicrobials and different formulations would be expected to have some level of effectiveness, the number of flights needed to detect statistically significant differences would be considerably larger. Future studies should consider testing alternative antimicrobials and varying formulations.

2. Interpretation of Study Findings

Phase I-Glove Juice Test:

Those assigned to hand-cleaning regimes containing antimicrobial agents had significantly greater reductions in hand colony counts from baseline levels than those assigned to placebo and no treatment groups. No significant reductions were, however, noted when soap containing triclosan soap was added to the hand-cleaning regime. This finding was somewhat surprising. In theory, the addition of an antimicrobial soap to the handwashing regime should increase the amount of time the subject spent cleaning his hands and produce some additional lowering of hand colony counts. Other studies have reported increased reduction in colony hand counts associated with the increasing length of the time spent accomplishing handwashing [81-83]. These studies, however, were designed to measure reduction in bacterial counts among physicians and nurses prior to surgical procedures. The subjects in this study were not greatly knowledgeable in

infection control procedures and likely did not wash their hands as thoroughly as would be expected of medically trained personnel. Another possible explanation for the lack of further reduction when triclosan soap was added could be related to the sequence in which handwashing and handwipe use were implemented. Since the recruit subjects were not specifically told to wash their hands first with triclosan soap and then apply the handwipes, it is possible that some reversed the order of application. If PCMX has an residual effect when left on the hands, handwashing immediately after application would likely eliminate this effect.

No significant differences were also noted between the hand colony counts of those assigned to placebo and those assigned to continue normal hygiene practices. As stated earlier, the glove juice tests, as applied in this study, focused on reductions in normal rather than transient bacterial flora. Consequently, placebo handwipes would not be expected to show any major effect on hand colony counts.

The consistent reductions in hand colony counts among all but the no treatment group when baseline and first post intervention samples were compared likely reflected the short term effects of the interventions employed. The 71.4 and 57.9 percent reductions seen among those assigned to antimicrobial agents is remarkably similar to those of other hand disinfectant studies testing PCMX when collections were made at the same intervals [53,57,84]. The fact that this level of reduction was not maintained at the second post intervention sample collection is reasonable considering that the intervention was applied at a rate of only four times daily. A rebounding of hand colony counts from those seen at

first post intervention collection would be expected given the hand contamination associated with normal daily activities.

An unexpected finding was the differences in average baseline hand colony counts among groups. These differences prompted adjustment for baseline counts in the final linear regression model comparing handwipe groups. These differences can likely be attributed to the relatively small study sample size (40 subjects) and the underlying wide variability in baseline bacterial load among individuals. While average baseline hand colony counts, along with gender, were confounders in this analysis, they did not influence appreciably the overall conclusion of the glove juice test.

While the glove juice test was intended as a decision making tool for phase II of the study, the basic principles of the test did not readily apply to this study. Future studies should consider either modifying the test to measure transient bacteria or selecting an alternative methodology.

Phase II-Field Test

The use of antimicrobial handwipes by recruits were associated with over a 30 percent reduction in initial sick-call visits for acute upper respiratory infection and a 40 percent reduction in initial visits for sore throat. Further, the results of throat culture specimens obtained at the beginning and end of the study showed that flights assigned to use antimicrobial handwipes had no change in the prevalence of GABS positive cultures while those assigned to placebo handwipes experienced a three fold increase. These findings provide strong support for the theory that the use of antimicrobial handwipes

contribute to reducing direct contact transmission of pathogens responsible for acute upper respiratory infections among recruits.

The acute upper respiratory infection sick-call rates reported in this study are consistent with those of other studies involving military recruit populations, [3-5,85] but are markedly higher than previously measured rates among Air Force trainees[7]. The most likely explanation for these higher rates is seasonal variation. While previously collected Air Force statistics were based on the collection of sick-call information over several months, this study involved a short two month interval during the height of the cold and flu season. That is why the rates observed in this study were expected to be somewhat higher than those previously reported. Additionally, the previously collected Air Force data were designed to trigger viral culture collection as part of an influenza surveillance program. Given the objective for which the data were collected, it is possible that cases were not as thoroughly investigated as in this study. Enthusiasm for the active reporting of acute respiratory cases by health care providers probably waxed and waned depending on the perceived influenza threat. The tabulation of acute respiratory cases in this study did not depend on health care provider reporting and the thoroughness of medical record review was maintained through the study. As such, it is likely that the results of this study more accurately reflect the acute respiratory rates for Air Force recruits during winter months.

Group A Beta-hemolytic *Streptococcus pyogenes* throat culture rates, on the other hand, may not reflect the true overall prevalence of this bacteria among recruits. Previous studies of GABS prevalence have shown initial rates of around three percent among

recruits and a doubling of the prevalence rate during the training period[86]. The approximately one percent baseline rate seen in this study is considerable lower. One possible explanation is a reduced recovery of GABS from oropharyngeal specimens due to collection and laboratory processing error. While laboratory processing errors are possible, due to the experience of the laboratory staff involved and the laboratory's quality control standards, they are unlikely. Reduced recovery of GABS organism during collection could explain the lower rates. However, since only one experienced staff member was involved in the collection of nearly all specimens, this scenario is also unlikely. Additionally, any errors associated with sample collection would have been nondifferentially applied to both handwipe groups. Thus, the proportional change in GABS prevalence was not appreciably affected.

Another explanation for the lower than expected GABS positive throat culture rates could be seasonal or chance variation. Supporting this explanation is the fact that the rate of streptococcal pharyngitis seen during this study was markedly lower than that seen among Air Force recruits in the past several years for the months in which the study was conducted. Regardless of the explanation, the internal comparison of GABS positive throat culture prevalence among handwipe groups in this study should be considered valid and evidence of an effect associated with handwipe type.

While significant reductions in upper respiratory infection and sore throat sick-call rates were noted among those flights assigned to antimicrobial handwipes, no differences were noted among trainee reported incidence of cold and/or sore throat. There are at least two reasons for this inconsistency. One is that many minor cases of cold and sore throats

not requiring medical attention occur among recruits and these cases are not attenuated by the use of handwipes. Another reasons for these findings may be that recruits are misdiagnosing some cases of allergic rhinitis as colds.

With respect to the first reason, it is apparent from the questionnaire results that that rate of colds and/or sore throats is much higher (84 cases/100 trainees) than the sick call rate (16 to 24 cases/100 trainees). Despite the availability of free medical care, recruits do not attend sick-call for every cold or sore throat. A review of recruit medical record showed that many are ill for several days before seeking care. Compounding this is the recruit's reluctance to lose training time while seeking medical care and face the risk of failing part of basic training. It is conceivable that different infectious agents are associated with these minor cases and that transmission of these agents is primarily airborne. While this scenario could explain these findings, it is hard to imagine that these infectious agents would respond differently with respect to the effects of antimicrobial handwipes. Even when infectious agents are transmitted primarily by airborne routes, some proportion of cases are likely contracted by direct contact. As such, observed differences between flights, by handwipe assignment, should be proportional to the degree in which the agents are transmitted by direct contact and their susceptibility to the antimicrobial agent. Either this study was not precise enough to measure these differences or there is another reason for the findings.

Another possible explanation is that recruits misclassified cases of allergic rhinitis as colds and/or sore throats. Allergic rhinitis is a particular problem in the San Antonio, Texas during the winter months[87]. The area north of the city called the hill country is

forested with abundant stands of cedar trees. During winter months winds shift to the north and blow allergens from the hill country into the city. Additionally, during the early months of the year, cedar trees are pollinating. This combination of events leads to a large number of cases of allergic rhinitis among the city residents. Recruits similarly suffer from allergic rhinitis with sick-call rates of approximately (9.2/100 recruits).

Efforts were made during questionnaire testing to ensure that the form adequately explained cold symptoms so recruits could differentiate between colds and allergies. It is possible however, that in the process of questionnaire implementation the recruits in the study did not read the questionnaire thoroughly before answering the questions. Delays between the times of illness and questionnaire completion could also play a role in misclassification. Since handwipe type would not be expected to have an effect on allergic rhinitis, the net result of such misclassification would be to mask any differences between handwipes type.

One remarkable finding in the questionnaire data, is the very high rate of reported colds and sore throats. Over eighty percent of recruits questioned reported experiencing what they considered to be a cold. Excluding short-term outbreaks, this rate is much higher than previously reported findings involving military recruits[3-7,88-90]. Although likely reflecting a considerable amount of misclassification, the fact that trainees recalled and reported their illness event, provides some insight into the extent of the problem of respiratory illness among military recruits. Whether the condition was due to an infectious agent or an allergen, these recruits became ill during training. This fact underlies the importance of continued study in this area.

An important finding from the questionnaire data relates to the medical care seeking behavior of those trainees who reported experiencing a cold. While not reaching statistical significance, among recruits with colds, those assigned to flights using placebo handwipes tended to seek medical care for their condition more often than members ill with colds in flights using antimicrobial handwipes. The most likely explanation for this difference is that those in flights using placebo handwipes were more severely ill. While the reason for the difference in illness severity can not be determined from this study, it is important to note that the findings associated with severity of illness agree with data from sick-call visits. The end result from both questionnaire obtained information on medical care seeking behavior and sick-call visit data is a reduction in the use of medical resources associated with antimicrobial handwipe use.

Another noteworthy finding from the questionnaire data relates to the level of handwipe use. While only approximately 50 percent of the recruits used handwipes more than 3 times daily and just over 50 percent used handwipes more than 3 days weekly, considerable reductions in sick-call visits and GABS positive throat culture prevalence were realized.

As depicted by figure four, protection from acute upper respiratory infection increased with more frequent use of handwipes. However, some protection was provided by even infrequent use of handwipes. For those diagnosed with sore throats, the protection afforded from increasing frequency of handwipe use is not so clear (figure 5). It appears that even limited use of handwipes affords good protection against sore throats. Two factors help explain these findings. First, those who used handwipes at minimal

levels were not in a vacuum. They were primarily exposed to other recruits who were using handwipes more frequently. Consequently, while their personal level of protection was probably reduced due to less frequent antimicrobial handwipe use, the cumulative dose of acute respiratory pathogens within the entire flight was reduced. The resultant effect was reduced exposure to these pathogens and a lower illness rate.

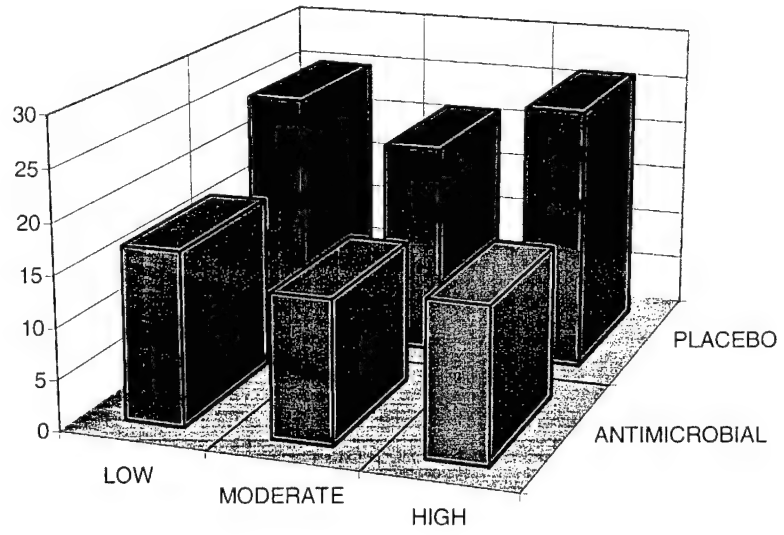
The second factor deals with the prevalence of specific pathogens within the flight and the susceptibility of these pathogen to PCMX and alcohol. Sick call visits with a diagnosis of pharyngitis made up only a small subset of all acute upper respiratory infection associated sick -call visits. This finding would argue that the infectious agents responsible for cases of sore throat are less numerous than other infectious agents. Therefore, the effect of even minimal use antimicrobial handwipes may be to reduce exposure to below infective does levels. With respect to susceptibility, initial studies conducted with PCMX showed remarkable reductions in streptococcal organisms [52]. If other agents associated with pharyngitis are similarly susceptible, the lack of a strong dose response associated with frequency of handwipe use could be explained.

With an annual recruit population of 30,000 trainees and an acute upper respiratory infection incidence rate of 24.1 initial sick-call visits per 100 recruits, the results of this study indicate that 2370 initial medical visits could be eliminated through the use of antimicrobial handwipes. At a cost of $53.95 per visit [91] and an average of 1.3 medical visits per initial acute respiratory sick-call case, this equates to a saving of over $166,000 in medical expenses. Providing three antimicrobial handwipes daily to 30,000 recruits for the length of their training period equates to an expenditure of approximately

$165,000 annually. While this analysis showed the handwipes to be cost effective, it does not take into account potential seasonal variations in cold and sore throat incidence nor does it address the logistical costs associated with providing the handwipes. Further, it does not put a dollar cost against the recruit training time loses due to colds and sore throats. The cost benefit analysis does however, provide reasonable assurances that the cost of providing antimicrobial handwipes would likely be offset by savings in medical expenses.

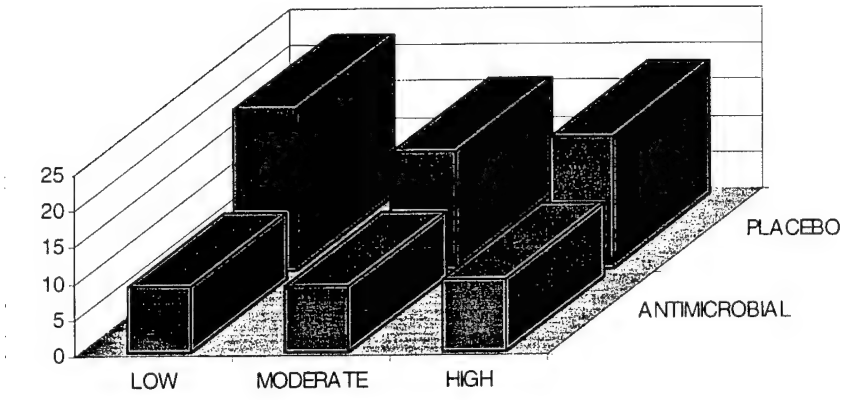
In conclusion, this study provides reasonable evidence of an association between the use of antimicrobial handwipes and reductions in medical visits for colds and sore throats among military recruits. Further an association between the use of antimicrobial handwipes and reduction in GABS positive throat culture prevalence was noted. To the author's knowledge this is the first study to provide clinical evidence of the efficacy of such a hand-cleaning method in a community based population. The results from here are directly applicable to military recruits; a cohort known at high risk for infectious diseases. Others may also benefit from these results. Children in day-care and preschool environments suffer from increased incidence of upper respiratory disease and frequently do not practice optimum hand-cleaning standards. Nursing home residents could realize similar benefits. While the results of this study are not conclusive in that only one antimicrobial formulation was tested in a rather special high risk population, the findings provide considerable promise that antimicrobial handwipes can effectively reduce human suffering due to colds and sore throats.

Figure 4. Acute upper respiratory infection sick-call visit rate measured in initial visits per 100 flight members for U.S. Air Force recruits among three levels of handwipe use comparing antimicrobial to placebo handwipes.



Low = 1 to 5 handwipes weekly
Moderate = 6 to 14 handwipes weekly
High = 15 + handwipes weekly

Figure 5. Sore throat sick-call visit rate measured in initial visits per 100 flight members for U.S. Air Force recruits among three levels of handwipe use comparing antimicrobial to placebo handwipes.



Low = 1 to 5 handwipes weekly
Moderate = 6 to 14 handwipes weekly
High = 15 + handwipes weekly

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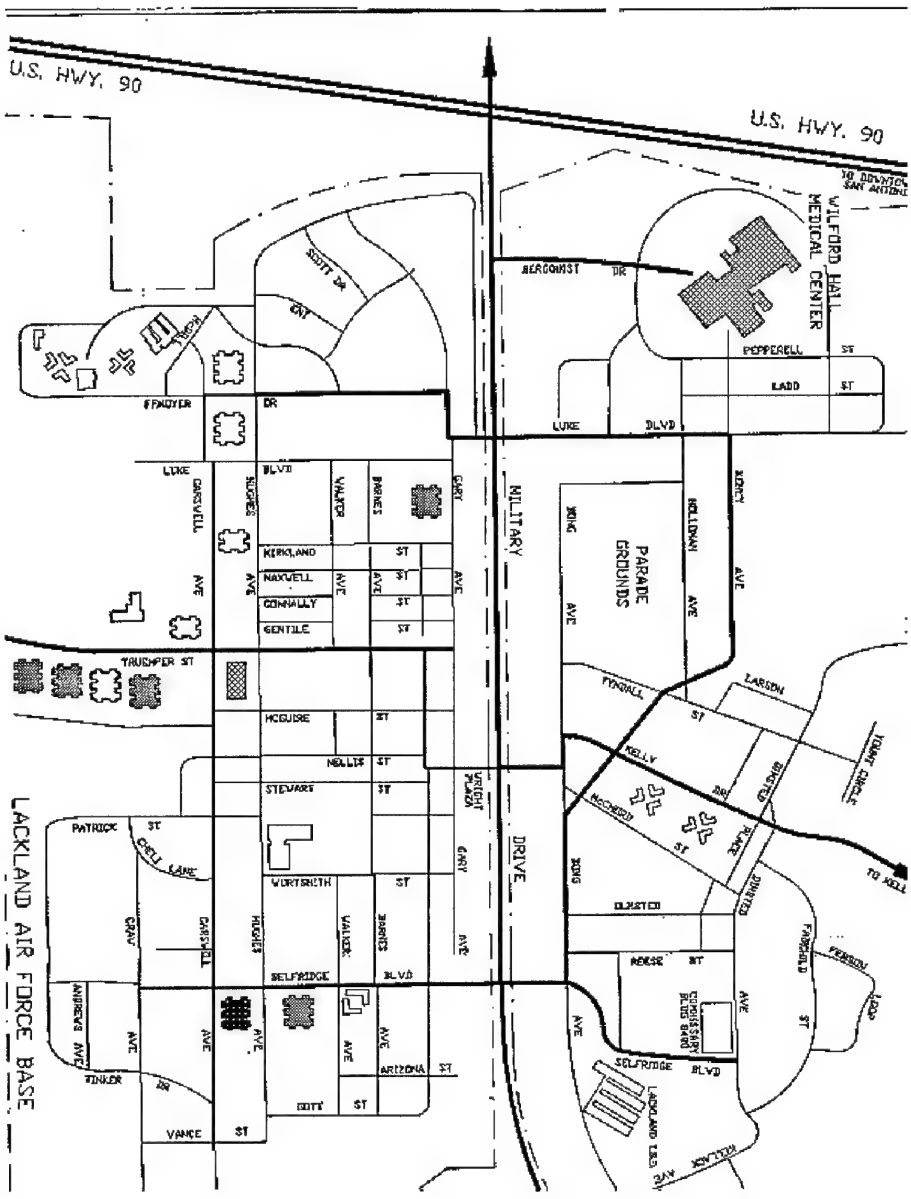
Appendix A: Map of Lackland Air Force Base, Texas with training squadrons, Medical Hold squadron and medical facilities highlighted.



Legend:

- Training Squadron
- Medical Hold Squadron
- Medical Facility

Appendix B: Glove Juice Method Instructions

1. Prepare the following two solutions prior to performing the glove juice tests

Neutralizing Solution:

Lecithin		30 g
Lubrol PX		100 g
$Na^2S^2O^3$		20 g
Tween-80		25 g
Sterile purified water	Total	1000 ml

Sampling Solution:

Na^2HPO^4		10.1 g
KH^2PO^3		0.4 g
Triton X-100		1.8 g
Sterile purified water	Total	1000 ml

2. Hands are washed using CAMAY® soap, adhering to the following protocol:

a. Moisten the hand, fingers and the forearm with sterile water
b. Make foam with the soap in the palms for 15 seconds
c. Wash the lower two-thirds of the forearm for 30 seconds
d. Rinse off with sterile water for 15 seconds
e. Shake off excess moisture

3. Washed and autoclaved surgical rubber gloves are placed on both hands of the subject.

4. Into the right glove, 5 ml of neutralizing solution and 25 ml of sampling solution is poured.

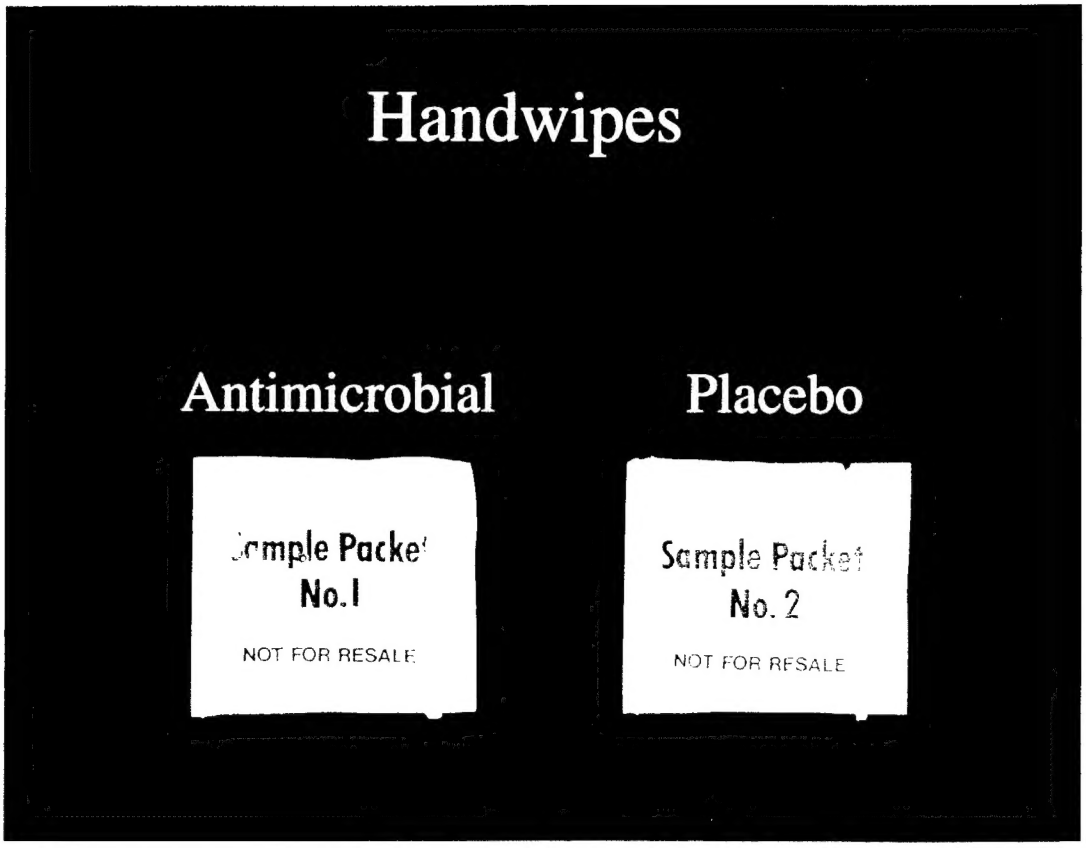
5. While the subject holds the top of the glove, an assistant massages the hand for 1 minute.

6. The glove is removed taking care not to let the solution in the glove flow out and the sample is collected in a sterilized tube.

7. The procedure is repeated on the left hand.

8. Samples of the glove juice collected from the right and left hands are diluted 10- and 100- fold. Using Conradi's bar, 0.1 ml of each dilution is smeared onto blood agar medium and incubated at 32°C for 48 hours. The number of colonies formed are counted and converted to the total number of cells in the sampling solution. Bacteria are identified according to standard laboratory methods.

Appendix C: Examples of handwipes used in the field trial



Appendix D: Prevention of colds and sore throats questionnaire

PREVENTION OF COLDS AND SORE THROATS QUESTIONNAIRE
(Operation Tiger Claws)

The questions asked on this form are designed to determine if the handwipes you used during basic training helped to prevent colds and sore throats. Use the **RED SIDE** of the OMR classroom answer sheet to record your answers. DO NOT WRITE ON THE QUESTIONNAIRE.

On the line marked NAME, **PRINT** your LAST NAME and the STATE you lived in when you entered basic training.

In the boxes marked IDENTIFICATION NUMBER, starting on the LEFT, write your SOCIAL SECURITY NUMBER. Fill in circles accordingly.

A cold is defined as an illness where you have a runny nose and usually a cough. You fell tired. a little weak, and sometimes your muscles are sore. When you blow your nose, the drainage can be clear but often it is thick and yellow or green. You can have a fever and a headache with your cold but just having these symptoms without a running nose or cough is not considered a cold. Having itchy and burning eyes with a runny nose where the drainage is clear and thin is usually not a cold. You can also have a sore throat with your cold and sometimes you have a hoarse voice. For the purposes of this questionnaire, colds and sore throats are treated separately. Questions 1 through 3 ask about colds that occurred with sore throats. Questions 4 through 6 ask about colds that occurred without sore throats. Questions 7 through 9 ask about sore throats that occurred without colds. All these questions refer to colds and sore throats caught DURING Basic Training. DO NOT record information on colds or sore throats you may have caught prior to starting training.

COLDS WITH SORE THROATS

1.	Did you get a **COLD** (with a sore throat) during basic training?	1	=	Yes
		2	=	No
2.	How many times did you get a cold (with sore throat)?	1	=	Once
		2	=	Twice
		3	=	More than twice
		4	=	Didn't get a cold with sore throat
3.	Did you seek medical care for a cold (with sore throat)?	1	=	Yes
		2	=	No
		3	=	Didn't get a cold with sore throat

COLDS WITHOUT SORE THROATS

4.	Did you get a **COLD** (without sore throat) during basic training?	1	=	Yes
		2	=	No
5.	How many times did you get a cold (without a sore throat)?	1	=	Once
		2	=	Twice
		3	=	More than twice
		4	=	Didn't get a cold without sore throat
6.	Did you seek medical care for a cold (without a sore throat) ?	1	=	Yes
		2	=	No
		3	=	Didn't get a cold without sore throat

TURN OVER⇒

SORE THROATS WITHOUT COLDS

7.	Did you get a **SORE THROAT** (without a cold) during basic training?	1	=	Yes
		2	=	No
8.	How many times did you get a sore throat (without a cold)?	1	=	Once
		2	=	Twice
		3	=	More than twice
		4	=	Didn't get a sore throat
9.	Did you seek medical care a sore throat (without a cold)?	1	=	Yes
		2	=	No
		3	=	Didn't get a sore throat
10.	What week of training did you get your FIRST cold (with or without a sore throat)?	1	=	Week 0 or Week 1
		2	=	Week 2
		3	=	Week 3 or 4
		4	=	Week 5 or 6
		5	=	Didn't get a cold
11.	What week of training did you get your FIRST sore throat (without a cold)? cold)?	1	=	Week 0 or Week 1
		2	=	Week 2
		3	=	Week 3 or 4
		4	=	Week 5 or 6
		5	=	Didn't get a sore throat
12.	How many times a day did you usually use your handwipes?	1	=	Once
		2	=	Twice
		3	=	Three times
		4	=	Four or more times
		5	=	Didn't use the handwipes
13.	How many days a week did you usually use the handwipes?	1	=	1 or 2 days weekly
		2	=	3 or 4 days weekly
		3	=	5 to 6 days weekly
		4	=	Everyday
		5	=	Didn't use the handwipes
14.	Do you have a sore throat today?	1	=	Yes
		2	=	No
15.	If you have a sore throat, on a scale of 1 to 4, how bad does your throat feel today?	1	=	Just a little sore
		2	=	Hurts
		3	=	Hurts a lot
		4	=	Really sore
		5	=	Do not have a sore throat
16.	Did you have a cold or sore throat when you started Basic Training?	1	=	Yes
		2	=	No
17.	What do you consider as your race?	1	=	White
		2	=	Black
		3	=	Hispanic
		4	=	Asian
		5	=	Other
18.	Did your hands become excessively dry, or sore during Basis Training?	1	=	Yes
		2	=	No